**The Physicians Approach to Biotoxin Illness**

4/24/14

Inflammation and Chronic Fatiguing Illness Ritchie C. Shoemaker MD 4/9, 10/11

[www.survivingmold.com](http://www.survivingmold.com).

[Keith Berndston MD's Mold Toxicity Syndrome/CIRS Slides](http://www.slideshare.net/keithberndtson/mold-toxicity-syndrome-cirs) provide additional information.

**Hopkinton Drug Compounding and Wellness**

(508) 435-4441 [www.rxandhealth.com](http://www.rxandhealth.com)

[**Diagnostic Laboratory Panel**](#ChartDrawSheet)

[**CIRS Treatment Protocol**](#CIRSTreatmentProtocol)

[**SAIIE; Timeline of Abnormalities in the Sequential Activation of Innate Immune Elements**](#SAIIE)

[**Visual Contrast Sensitivity Technique**](#VCSTechnique)

[**C4a Effects**](#C4aActions)

[**VIP Trial Protocol**](#VIPTrial)

[**VIP Results**](#VIPResults)

[**Summary of Lab Tests**](#SummaryofLabTests)

[**Patients PMH Questionnaire; Clues to CIRS**](#PMHCluestoCIRS)

[**VIP Dosage, Effects & Restrictions**](#RANGE!D13)

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1. **Getting Started**
   1. What illnesses are we talking about?
      1. Mold, Post-Lyme, Fibromyalgia, Chronic Fatigue Syndrome (CFS)
         1. Stachybotrys forms [Tricothecene toxins](http://www.slideshare.net/keithberndtson/mold-toxicity-syndrome-cirs)
            1. T2 toxin (associated with “yellow rain”
            2. Satratoxin H (SH)

Disrupts brain endothelial cells/blood-brain barrier

Induces initial anti-inflammatory response from astrocytes.

Chronic exposure results in local oxidative stress & neuronal apoptosis C/W lupus, MS, Alzheimer’s

Chronic immune response to inhaled SH may produce neuronal hypersensitivity/damage additive to exposure to other airborne toxins/inflammagens.

* + - * 1. Tricothecene Toxicity Mechanisms

Cell-cycle arrest

Mitosis disruption

Protein synthesis inhibition

Oxidative cell stress with DNA damage

Cell membrane disruption/permeability

Immunodysregulation (stimulation & suppression)

Apoptosis induction

Increased expression of inflammatory & apoptotic mRNA’s

Ribotoxic stress response producing MAPK induction of cytokine release

Endotoxic reticulum stress with protein misfolding & blocked unfolding

* + - * 1. Toxic Bioaerosol Dispersal

<2% of mold toxins are attached to mold spores; they are free-floating particles dispersed by vibration & air turbulence

Mix with volatile organic compounds (VOC) and are major threats to indoor air quality

* + 1. Ciguatera, Cyanobacteria are not rare
    2. Gulf War Syndrome (GWS)? Gardasil? LymeRx?
    3. Few physicians have an organized approach to Dx & Tx
    4. CIRS; (Chronic Inflammatory Response Syndrome)
    5. The answers come from data!
  1. Water Damaged Buildings (WDB) are a continuing problem.
     1. Discolored carpet
     2. Musty smell
     3. Stained walls/ceilings
     4. Smell of Volatile Organic Compounds (VOC’s)
     5. Do they have high water bills from a possible “pin-hole” plumbing/water pipe leak inside a wall
     6. This interior environment is a complex ecological system with multiple potential sources for inflammation.
        1. These potential sources of inflammation will make people sick if they are damaged by and/or susceptible to innate immune responses from pre-existing illness.
        2. Illnesses in I-A (above) have a final common pathway, which lets us identify “what is wrong with them now”.
        3. That is what we treat!
           1. Not what was wrong with them in the past
  2. Ciguatera will occur even in northern cities due to air-freight bringing seafood from the tropics to northern locations
     1. Grouper, Amberjack, Barracuda
     2. While gathering their history, ask them; “Do you eat fish?” If not, then Ciguatera is low on the list of probable causes.
     3. If they eat fish; “Do you ever get sick while eating fish?”
        1. GI, Cardiovascular and skin symptoms, heat/cold reversal esp. around lips followed by chronic fatigue that doesn’t resolve over 3-6 mos.
  3. Cyanobacteria can even occur in cold latitudes esp. in summer when rivers dry up, but less likely there.
     1. Exposure to shellfish beds; Brevitoxin 2,3,9
  4. LymeRx Vaccine has caused problems;
     1. What happens if we give people a known agonist of Toll-2 and Toll-4 receptors
        1. Which group of people is sickened if given Toll-2 or Toll-4 Receptors?
        2. [HLA-DR4](http://www.tequestafamilypractice.com/articles/CIRSHLA.htm) folks are susceptible, DR4 is actually a Haplotype of 43-53
        3. DRB 1-4 has 12 subtypes
        4. 0401 has the worse illnesses
     2. Some of these subtypes are a different type of CFS,
        1. They’ll have lots of things wrong with them.
  5. Gardasil vaccine
     1. 11-3-53 Haplotypes should avoid this vaccine
        1. Only about 1% of the population

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1. **Chronic Inflammatory Response Syndrome is the common pathway to all of these.**
   1. Chronic Immunologic, Rheumatologic, autoimmune diseases, keep an eye out for the problems that are a subset of CIRS
      1. Absence of regulatory neuropeptides is the final common denominator.
      2. Lack of regulation is a vital concept
         1. Genes load the gun, exposures pull the trigger.
      3. Cast out false knowledge
      4. Each of these illnesses has a lot of history of opinions and treatments but no consistent protocol for therapy
      5. Until recently, there were no biomarkers
      6. Each is readily identified by innate immune inflammatory responses in the setting of the absence of normal neuropeptide regulation.
      7. We now have biomarkers that let your work be transparent and reproducible.
   2. [Biotoxin Pathway](http://www.survivingmold.com/diagnosis/the-biotoxin-pathway);
      1. [MSH](#MSH) (Melanocyte Stimulating Hormone)
      2. [VIP](#VIP) (Vasoactive intestinal peptide)
      3. Vasopressin/Osmolality regulation
      4. All interact in the hypothalamus.
      5. Defining what is wrong (brings effective treatment);
         1. Regulation of dysregulated systems is necessary
         2. We need to start lowering levels of the elevated levels of inflammagens;
         3. C3a and C4a are anaphylatoxins. C3a reacts to bacterial membrane molecules. C4a reacts to biotoxins. Lyme disease can raise C3a and C4a levels. CIRS-WDB raises C4a and tends to lower C3a.
            1. C3a
            2. [C4a](#C4a)

C3a & C4a can help differentiate between acute Lyme and post-Lyme

C4a is important in looking at cognitive effects such as brain fog, executive cognitive function, reduced efficiency of recent memory, difficulty with concentration & word finding, confusion, disorientation.

Effect is exerted via *capillary hypoperfusion* in the brain.

[(i) Coagulopathies (correctable with DDAVP/Desmopressin by enabling fibrin monomers to form multimers)](http://www.slideshare.net/keithberndtson/mold-toxicity-syndrome-cirs)

* + - * 1. [MMP9](#MMP9)
        2. [TGF β-1](#TGFB1)

When TGF β-1 issues are fixed, autoimmunity resolves.

Stimulated by a variety of cell types, not just [HIF](#HIF) (Hypoxia Inducible Factor)

Will down-regulate VEGF

* + - * 1. HIF turns them both on, TGF β-1 is slow to react; down-regulates VEGF
      1. Correct hormonal dysregulation
         1. If estradiol is elevated, consider an aromatase inhibitor.
         2. MSH deficiency commonly causes hormonal issues.
         3. ACTH-Cortisol
      2. Deal with autoimmunity
         1. Look for anti-gliadin antibodies
         2. Anti-cardiolipin antibodies [(ACLA)](#ACLA)

Spontaneous abortions in women of reproductive age, first trimester fetal loss

Also, lack of MSH will do this.

Mycotoxic exposures can also cause this.

* + - 1. Improve capillary hypoperfusion
         1. What happens to a cell if you starve it but don’t kill it?
         2. Inadequate *delivery* of oxygen does not mean the problem is due to mitochondrial dysfunction.
         3. Inadequate delivery of sugar and other metabolites doesn’t mean that there is a primary metabolic disorder.
         4. Hypoperfusion will cause reduced glycogen content in muscle and other organs as well as protein wasting
      2. Eradicate commensal staphs
         1. A multi-headed beast
         2. Biofilm forming coagulase negative Staph

Produce exotoxins that split MSH

Make hemolysins that set off cytokine responses

Lower T-Regulatory cell counts as well

If an aerobe such as staph living in the sinuses can do all of these things, what happens in the gut?

There are lots of commensal’s there too!

Are they altering our host innate immune responses?

Of course they do; look at Ulcerative Colitis!

When TGF β-1 is corrected, the patient will convert their ANCA’s to negative.

What set it off to begin with?

* + - * 1. These staph don’t cause allergic, infectious symptoms;

Cannot survive without adequate MSH.

What would happen if MSH were added to Biofilm forming Staph?

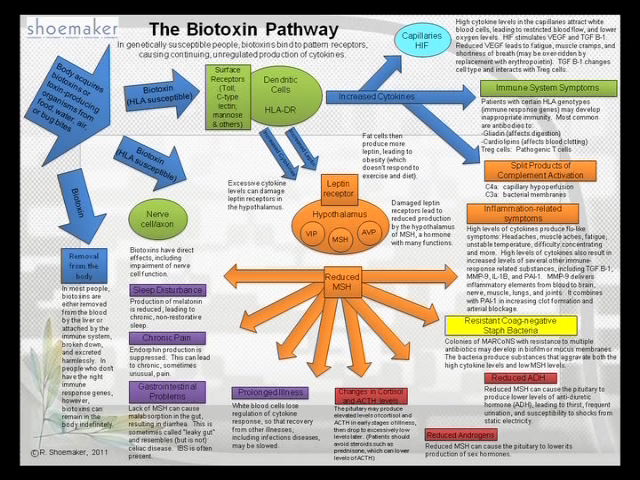
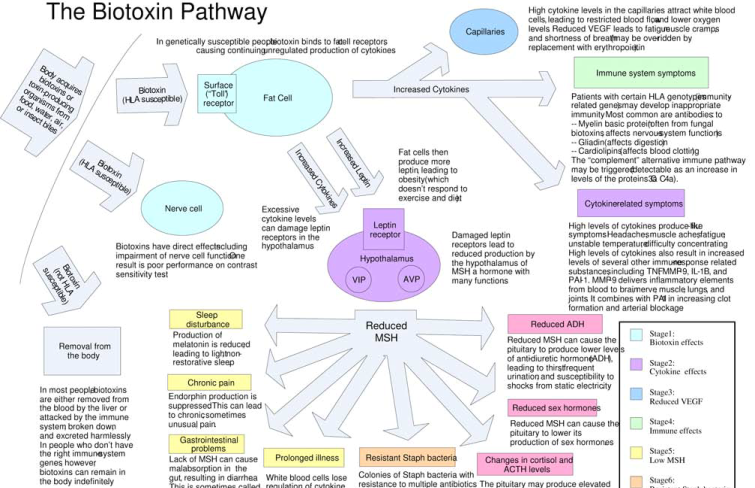
Syngen, a pharmaceutical company

Topical MSH wipes out Candida and others

* + - 1. Correct cellular immunity
         1. Dr. Lewis Thomas, 1974, unaware of C4a yet talks of complement activation, didn’t know about TGF β-1 but talks about the many host responses that become a disease related to poor capillary perfusion.
  1. Please stop guessing!
     1. Assumptions destroy good medicine
        1. “Thou shall not assume!” (The 11th Commandment!)
        2. Use objective parameters
        3. Symptoms alone are non-specific
           1. They’ll tell you *something* is wrong, not *what* is wrong
           2. Many of the illnesses listed in A-1 above cause the same symptoms, but all have different causalities and therapies
           3. Symptoms don’t ensure causation of complex multisymptom illness
           4. The field of chronic fatiguing illnesses is filled with assumptions
           5. Let’s stop such nonsense; the data from reliable labs will set you free!
        4. Assumptions of assumptions are fatal to chronic illness management
           1. Ass2
        5. Psychiatric diagnosis are the worst, with Fibromyalgia a close second
        6. “You look good, you couldn’t be ill”
        7. “All labs are normal”
        8. Reliable labs;
           1. LabCorp & Quest frequently change their “normal” ranges
           2. “Alternative” labs may not have reproducible data—run the same test several times on the same patient sample—the results should be very similar…
           3. “Split-Samples” can help you decide if lab is good or not; submit same specimen more than once, beware of result disparity
     2. Hunting in the dark with a hammer?
        1. A flashlight is a better idea
        2. Let there be light
        3. High light/heat ratios
        4. Always challenge today’s hypothesis tomorrow
           1. Eg; Cellular Immunity
        5. Knowledge is dynamic
           1. Changes daily with new research findings
        6. Understanding is basic
  2. Systems Approach
     1. In depositions, the non-systems approach is used; “You are not a toxicologist, an immunologist, a pulmonologist, a geneticist, an epidemiologist, a rheumatologist, a neuroradiologist or any other specialty are you?”
     2. Glean from it all! Absence of a systems approach will guarantee all the specialty care fails to understand the whole picture.
     3. The unit of care is the person, not an individual organ system
     4. Wooded wetlands can teach you, all you need to do is listen:
        1. Tell the transition zones by the shifts in vegetation
        2. Strength of the forest mat of intertwined root systems; take out one element of the system and the entire system fails
        3. Disrupt one element of a food chain by our actions and watch for disaster
        4. Ecosystems show us systemic thinking!
        5. There will be different “ecosystem” effects in people with the changes wrought by the Chronic Inflammatory Response Syndrome; changes in MSH, TGF β-1 /low VO2max, VIP etc. It all needs to be re-regulated and brought back into balance!
  3. Human Ecology;
     1. Who we are, our genetics, changes our response to…
     2. Where we are, our environment
     3. Creating what we are in health
     4. Complex, interacting, ever-changing
     5. Influence of what happened to us a year ago affects what will happen to us tomorrow.
     6. Why is man created to deteriorate, “suffer and die”?
        1. Why not?
        2. What is causing the suffering?
           1. We’re not looking at the “terminal decay at the end of life”, we’re looking at correctable illnesses.
        3. When is illness irreversible?
           1. Inflammatory problems are reversible!
        4. Goal is then to intervene to stop the pathophysiology, restore health.
        5. Goal in “my illnesses” is to restore regulation.
        6. But first, we must stop inflammation!
     7. Traditional model of chronic illness;
        1. Cancer, trauma, acute infectious diseases—don’t apply here
        2. Degenerative processes are inevitable
           1. Result of small changes adding up over time
           2. Htn, ASCVD, DM, COPD, OA, Osteoporosis, Cognition
        3. Yet, these ideas ignore inflammation
     8. Biotoxin Symptoms; (many unusual symptoms)
        1. Fatigue, weak
        2. Ache, cramps
        3. Unusual sharp, claw, electrical pains
           1. May have high osmolalities and low ADH activity with polydypsia, polyuria, extra salt thru sweat🡪elevated sweat chloride test!
           2. Clawed digits; tetanic contractures in muscles in end-circulation with buildup of lactic acid🡪capillary hypoperfusion
        4. Light sensitivity, red, blurred, tearing
        5. SOB, Cough, Sinus
        6. Abdominal Pains, Secretory diarrhea
        7. Joints, morning stiffness
        8. Executive, cognitive, memory, concern, word-finding, assimilation, confusion, disorientation
        9. Mood, Appetite, sweats, Temperature regulation
        10. Thirst/polydypsia, polyuria, Shocks
        11. Paresthesias, taste disturbances
        12. Vertigo, tremors, skin changes
        13. Look at “cluster analysis” with logistic regression with Visual Contrast Sensitivity scores
     9. Symptom Cluster Analysis; (common in Biotoxin illnesses, check MSH/C3a/C4a/TGF β-1)
        1. Fatigue
        2. Weakness, poor assimilation, aching, headache, light sensitivity
        3. Memory loss, dysphasia
        4. Impaired concentration
        5. AM stiffness, joints, cramps
        6. Unusual skin sensations, paresthesias
        7. SOB, sinus
        8. Cough, thirst, confusion
        9. Appetite, body temperature regulation, urinary frequency
        10. Red tearing eyes, blurred vision, sweats, mood, ice pick pains
        11. Abdominal pain, diarrhea, numbness
        12. Tearing, disorientation, metallic taste
        13. Static shocks, vertigo
     10. No biomarkers mean No data!
         1. Critics can call the illnesses medically uncertain
         2. Critics can and do label patients and providers as wacko’s
         3. “GOMER”
         4. Litigation, Secondary gain
         5. Munchausen’s; folie a deux
         6. Revisit the idiocy of assumptions

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2. [**Biotoxin Pathway**](http://www.survivingmold.com/docs/biotoxinpathway.pdf) **Overview:**

<http://www.survivingmold.com/docs/biotoxinpathway.pdf>



* 1. Data answers the critics
     1. 8,400 patients in one practice
     2. 14 collaborating physicians
     3. Data collection is updated daily
     4. Labs used are all based on literature, new labs will certainly emerge
     5. Number of Published Clinical Trials; 14 studies total by RCS
        1. Mold (6 studies)
        2. Ciguatera (1 study)
        3. Cyanobacteria (1 study)
        4. Lyme (2 studies, including Babesia)
        5. Pfiesteria (Dinoflagellates) (4 studies, including Grand Rounds in EHP)\*
           1. \* Double-blinded placebo controlled trial
     6. Pending Papers
        1. HLA DR defines environmental genetic interactions in Biotoxin illness
        2. VIP clinical Trial
        3. T regulatory cells in TGF β-1 illnesses
        4. Rx C4a and MR Spectroscopy
        5. How about the collaborative study on VIP? Everyone here ready?
  2. Innate immunity is old, but it isn’t
     1. System of antigen detection and inflammatory response is over three billion years old such as TOLL receptors
        1. 1989 Yale, first big studies in innate immunity
        2. This study is <30 years old!
        3. Evolutionarily conserved in mice, men, sea squirts and slime molds
        4. Look what came first; blue-green algae, fungi, Dinoflagellates, spirochetes.
        5. Look at the illnesses
     2. Look for the Final Common Pathway:
        1. Abnormalities in innate immune responses (non-specific for cause)
        2. Call it the “host response”
        3. Incredible amplification of multiple pathways following initiation
        4. CHRONIC INFLAMMATORY RESPONSE SYNDROMES!
        5. No single abnormality defines CIRS, look at all eight factors
  3. Don’t forget this is the *host response*
     1. How many molecules does it take to set off the inflammatory cascade?
        1. Maybe 6,000 total molecules!
        2. 1X10-23 grams!
        3. Classical equal and opposite physics is not exponential biology
        4. Cytokines, Complement, Cell-Mediated Immunity, Capillary hypoperfusion, tissue regulation of T-regulatory cells, coagulation; all ongoing and interacting.
        5. Check VonWillebrand profile
  4. CIRS is systemic, interacting…
     1. There is no way to say just one lab result is the source of fatigue, cognitive abnormalities, joint and respiratory problems
     2. All of the putative diagnosis’ have the *same final common pathway*
     3. You will see the same combination of multisymptom illness and labs
     4. Differential diagnosis is key!
     5. Coagulation abnormalities
        1. Check VonWillebrand’s profile
           1. Factor 8 is an acute-phase reactant; will be either hugely elevated or very low
           2. Ristocetin associated cofactor; will be either hugely elevated or very low
           3. VonWillebrand’s Antigen; will be either hugely elevated or very low

With Low Ristocetin associated cofactor and high C4a from a moldy environment, the combination will prevent the ability of the VonWillebrand’s factors to make a multimer to allow coagulation.

This will frequently cause mucosal bleeding

With normal C4a, multimerization will occur

This is an *acquired* VonWillebrand’s syndrome!

It’s part of the CIRS complex

* 1. CIRS
     1. Once you recognize it; your life as a physician will be changed forever
     2. Lack of *regulation* of inflammation
     3. Enhanced innate inflammatory parameters
        1. C3a
        2. C4a
        3. TGF β-1,
        4. MMP9
        5. And more
     4. Hormonal dysregulation
     5. Hypoxia from capillary hypoperfusion Low VO2max
     6. T-regulatory dysfunction
     7. MARCoNS
        1. Multiple antibiotic resistant coagulase negative staph
        2. Drop “a” to make it MRCoNS if methicillin resistant only
        3. Of the MSH-deficient patients, 80% will have MARCoNS
           1. Of those MARCoNS, 60% will be methicillin resistant
        4. Remember that Coagulase negative staph (Eg. Epidermidis) and Coagulase positive staph (aureus) get together and exchange plasmids
           1. Plasmids for antibiotic resistance are generated by the differentiation of these previously planktonic motile forms within Biofilm.
           2. We don’t have a good way to stop the plasmids within the biofilms.
           3. Coagulase negative staph is a huge reservoir of these plasmids just waiting to be inserted into more pathogenic organisms.
     8. Colonizing commensal MARCoNS
     9. VonWillebrand’s factor-66% abnormal: Acute reactants? NO.
     10. Autoimmunity like crazy!
         1. [AGA](#AGA), [ACLA](#ACLA), ANA, ANCA, Actin
         2. If a (+) ANA, check their [TGFβ-1](#TGFB1) which should be high, measure these parameters until they resolve
         3. ANCA elevated with TGF β-1 elevations
         4. Cellular immunity: TGF β-1
         5. Activated complement split products (C3a, C4a)
     11. Environment and genetics is a big deal!
         1. SNP studies abound (so what!)
         2. What prospective data do we have using genetic basis for susceptibility?
         3. Where can we link genetics in the pathophysiology of susceptibility?
         4. What can we access now using labs that are commercially accessible?
         5. The concept of susceptibility truly begins with genetics.
     12. What is the genetic basis of susceptibility to biotoxin illness?
         1. Look at [HLA DR](http://www.tequestafamilypractice.com/articles/CIRSHLA.htm)
         2. Immune response genes
         3. Chromosome 6
         4. Two copies code for a recognition structure
         5. Inside dendritic cells; in the surface of macrophages and lymphocytes.
         6. HLA is a marker on the cell surface for macrophages and monocytes to help them to identify a particular antigen.
            1. With high IL-10, HLA presentation is suppressed. IL-10 is an anti-inflammatory T2 suppressor, it’s not anti-inflammatory as much as it is *immune paralytic*
            2. It removes the detection mechanism
     13. Antigen presentation process
         1. Binding to receptor on dendritic WBC
         2. Phagocytosis (a primitive component of innate immunity!)
         3. Endosome must be acidified to open it up and allow…
         4. Fusion with lysosome to produce an endo-phago-lysosome which then
         5. Fuses with endoplasmic reticulum forms a “processed antigen” then is…
         6. Presented to naïve T cell and
         7. Presentation to B cell
         8. This pathway can be interrupted many different ways;
            1. Polycyclic ethers, such as dinoflagellotoxins, block the acidification of the endosome.
            2. Environmental acquisition of insulin resistance such that insulin receptors are taken into cells such as hepatocytes which creates an endosome but in the presence of moninsin or nigerisin (both are dinoflagellotoxins) preventing the release of insulin and monosaccharide which would allow monosaccharide delivery to glycogen for polymerization.

Moninsin is added to chicken feed.

It’s a compound that kills small predators called Immeria which kills little chickens

100 mg of Moninsin added to the chicken feed is cheaper than vaccinating the chicks against Immeria

Insulin resistance can occur up the food chain when the Moninsin treated chicken is consumed.

Remember that insulin is an inflammatory agent

Prolonged cooking can reduce glycemic index of foods

*Moninsin causes insulin resistance!*

Physicians advise patients with insulin resistance to avoid red meat and eat more chicken!

Even organic chicken may have Moninsin

Range-fed chicken is probably OK

* + 1. There are countless ways to go wrong
       1. Receptors must recognize the antigen
          1. Defective antigen presentation is the primary problem in this process.
          2. This problem stays with people once they become ill.
          3. The beauty of VIP is that once people become ill, it appears that VIP may reverse the defective antigen presentation problem that ill people have.
          4. VIP appears to do this by restoring regulation of the inflammatory process.
       2. Endosomes must be acidified
       3. HLA must be loaded onto the phagolysosome by the endoplasmic reticulum (role of autophagy)
       4. There must be clear binding to naïve T cells; this takes time
       5. Disrupted by CTL; can’t tell you about T to B cell
  1. What is *Susceptibility*? Simply put, it’s *Relative risk*
     1. An epidemiologic term
     2. Incidence in cases divided by incidence in controls (cases/controls)
     3. >/= 2.0 is what usually is required
     4. Several prominent studies from the CDC in CFS looked at 1.5
     5. 1.5 just wasn’t powered strongly enough statistically.
     6. Relative Risk by illness
        1. Looking at the 54 HLA DR Haplotypes
        2. Mold (CIRS-WDB) has 6 Haplotypes (24% of the total population)
        3. Lyme has 5 Haplotypes (21% of the total population)
           1. Infectious Disease Society of America references that about 20% of patients do not respond to antibiotic therapy (without paying attention to their haplotype).
        4. Ciguatera has 3 Haplotypes
        5. We have data on all 54 total Haplotypes
        6. Nothing in biology is 100%, BUT…
        7. If you have non-susceptible Haplotypes and get ill, prognosis is better, these patients are easier to treat, get better faster.
  2. DREADED GENOTYPES [(See Rosetta Stone document)](http://www.tequestafamilypractice.com/articles/CIRSHLA.htm)
     1. 4-3-53; 12 subtypes (3% incidence) (the worst RA, malaria, autoimmune hepatitis)
        1. -0401, -0402 and -0404 are the worst
     2. 11-3-52B (also 12-3-52B in labs) (1% incidence)
        1. Vaccine and long, tall, hypermobile, good athletes
     3. 14-5-52B rare but multisusceptible (0.1% incidence)
        1. Incidence is 3%, 1% and 0.1% respectively
     4. 13-3-52A is <0.05% incidence
     5. HLA DRB1-0401
        1. Worst C4a and worst TGF β-1 elevations
        2. Most commonly seen with multiple lab abnormalities
        3. Worst TB, Malaria, autoimmune hepatitis
        4. LymeRx vaccine (OspA)
           1. Experiment to see if defective antigen presentation actually hurt people
           2. >90% of those who had bad reactions to the LymeRx had this haplotype
        5. Even with these dreaded genotypes, the patient will be asymptomatic until they undergo a “priming event” that causes cytokine release
           1. Lyme disease or vaccine
           2. Mononucleosis
           3. EBF
           4. XMRV
           5. Coxsackie
           6. Enterovirus
           7. Kawasaki’s disease
           8. Pneumovax
           9. Yellow jacket stings
           10. Any other event that causes cytokine release
  3. Pfiesteria changed my world forever
     1. Who could help? No one
     2. Who could teach? No one
     3. Who can I believe from the state? No one (Sad)
     4. Who is deliberately trying to minimize the importance of altered environmental conditions?
     5. When the first big fish-kills started, the patients started coming in sick
        1. HA, myalgias, arthralgias, cough, memory problems, cognition etc.
        2. Secretory diarrhea—empiric use of Cholestyramine
           1. Cholestyramine can be compounded without Aspartame
     6. All other symptoms improved with Cholestyramine, so empiric Cholestyramine was started on everybody symptomatic
        1. All basic labs were negative
        2. Lung disease was restrictive, not obstructive as in asthma.
     7. Everyone said it was nutrients in the river (pollutants)
        1. Levels were unchanged
        2. An old mold, now resistant to standard fungicides was devastating crops exactly where fish kills occurred
           1. Use the old copper and Mancozeb (dithiocarbamate fungicide).
           2. Copper was being deposited along the distal bank of river bends (palustrine) linked with new plant growth in the pore water, copper was in the porewater of the mud, not in the free water column.
           3. Pfiesteria blooms occurred with the copper deposition
           4. Copper in the water column from the porewater was killing the Pfiesteria prey by allowing its prey to become free-swimming and motile
           5. Copper was also killing the nematodes that prey upon Pfiesteria
     8. Could fungicides be the source?
     9. Look to systems biology; find the copper in porewater at palustrine emergent vegetation sites exactly as the model said
     10. Confirmation came TEN years later!
     11. This illness was fascinating
         1. There were no clear physical findings
            1. The only way to make a diagnosis was by patient history
         2. Toxin binding with Cholestyramine helped clinically
         3. Capillary hypoperfusion was the clearly changing aspect (HRF & VCS) <http://www.survivingmold.com/store1/online-screening-test>
            1. The EPA for neurotoxicology studies approved the VCS; VCS showed deficits in Pfiesteria patients that weren’t found anywhere else.
            2. VCS was used as a biomarker, within three days of therapy it had improved, and typically within 2 weeks it normalized.
            3. VCS fell again with re-exposure to the source of the toxin
            4. Re-treatment resulted in restoration to improved or normal VCS
            5. Symptoms were demonstrated to be linked to reduce retinal capillary perfusion
  4. Lyme taught us about cytokines
     1. Lyme produced a toxin that diminished retinal capillary perfusion
     2. Cholestyramine actually worsened their symptoms of CIRS
        1. Measure [MMP9](#MMP9) (rising MMP9 is due to cytokine release-check it before starting antibiotics for Lyme as well), repeat [VCS](http://www.survivingmold.com/store1/online-screening-test); results will fall in rows E&D, recheck them after Cholestyramine dose 6 to 10).
        2. The intensification of symptoms and drop in VCS correlates with simultaneous cytokine release; “cytokine storm”.
           1. This is probably related to Cholestyramine binding toxin, temporarily reducing the amount of free toxin
           2. With lower free-toxin concentration, receptor-ligands to the bound toxin release resulting in rebound increase in free toxin and increase in symptoms with the cytokine increase from toxin binding to the dendritic cells.
     3. Pioglitazone, (Actos) also blocks cytokine production.
        1. Actos pretreatment for 5-10 days didn’t work without…
        2. Low amylase/low glycemic index diet given with Actos worked to block cytokine production/symptom worsening from cytokine Blocks
           1. TNF
           2. MMP9
           3. Plasminogen activator inhibitor-1 (PIE-1)
           4. Leptin levels decreased
        3. HLA yielded individual susceptibility
        4. Who ever heard of biofilm producers splitting MSH?
  5. Benomyl [(Agricultural uses of Benomyl causing resistance)](http://www.tequestafamilypractice.com/articles/Benomyl_Resistance.htm)
     1. Blocks of insertion of microtubules during anaphase of mitosis
        1. Benomyl blocks the insertion of the microtubule to the kineticore
        2. Mitosis becomes faulty, thus
        3. Benomyl is a potent mutagen; causing cellular mutations
        4. TGF β-1 microtubule mutations allowed fungi to overcome the Benomyl fungicidal/mutagen effect.
        5. Another mutation fungi experienced involving moving an acetyl group on the mycotoxin thus evolving a new mycotoxin that was not a native wild-type toxin
        6. The mutant fungus (Fusarium oxysporin select) producing the mutant mycotoxin produced cyanide in the rhizosome/fungal root which allowed Pseudomonas flourescens used the cyanide as an energy source
           1. This created an altered ecosystem in the soil
           2. Allowing P. flourescens to overgrow other soil consensuals
        7. People living in areas where this were occurring became symptomatic with CIRS
  6. Ecosystems and human health
     1. A lesson in systems biology
     2. Palustrine emergent vegetation with high nitrogen value located where the blooms were occurring
     3. Heavy metals deposited in porewater sites
     4. There was a huge availability of reduced copper compounds in the porewater sites
  7. Lyme changed a lot of early thinking about biotoxins
     1. Application of pure biotoxin theories to Lyme just doesn’t work
        1. There are other things going on with Lyme toxin
        2. These seem to involve cell-mediated immunity
        3. TGF β-1 (high levels are bad, therapy aims to reduce level)
           1. Turns on differential gene activation
           2. Affects autoimmunity
           3. Increases T-regulatory cell counts

Initially may appear to exert an *anti-inflammatory* effect; BUT

TGF β-1 actually converts T-regulatory cells to become pathogenic T cells/T-Effector Cells.

This drives a positive-feedback loop that continues tissue damage

This concept is more important in Lyme than many of the other conditions

* + - * 1. These T-effector cells then generate more TGF β-1
  1. Neurotoxins from Dinoflagellates, Cynaophyta (blue green algae/bacteria) and fungi all responded to Cholestyramine
     1. 1999 Dr. Donta shows a Lyme neurotoxin
     2. Lyme patient’s symptoms intensified
        1. What? Cytokine fluxes (MMP9)!
        2. Blocked by 5-10 day pretreatment with Actos (and/or high-dose omega-3 fatty acids)
        3. Actos only worked with a no amylose diet
     3. If Cytokines are involved with Lyme, what about other biotoxin illnesses?
        1. Cytokines are released by one cell to affect many others
        2. Labs for cytokines aren’t reliable
        3. Autocrine, Paracrine, Endocrine
           1. Autocrine effect; Cytokine activity on cells in an immediately adjacent site next to the cell releasing the cytokine
           2. Paracrine effect; Cytokine affecting nearby cells (i. & ii. Cannot be measured in blood tests, only iii. Can be measured).
           3. Endocrine effect; Cytokine affecting distant cells and tissues. (This is the only effect that can be measured with blood tests).
           4. Measuring cytokines themselves is thus flawed in terms of CIRS
  2. Measuring MMP9 directly measures the pro-inflammatory cytokine *effect* on receptors in endothelium and macrophages
     1. Cytokines are pre-formed and stored in intracellular vacuoles
        1. MMP9 is generated after pro-inflammatory cytokines bind to endothelial cells and macrophages which then…
        2. Initiate differential gene activation leading to the production of MMP14 which is then split to MMP9
           1. Interleukin 2 (IL-2) is another important mediator
        3. Sequence of events; Exposure to toxin🡪 symptoms if previously primed and HLA susceptible🡪turns on gene activation which leads to manufacture of a “pro-molecule” (MMP14) that is then split to the active compound (MMP9)🡪 CIRS.
           1. *The maximum time for generation of MMP9 after a point source exposure is between 2-3 days*
           2. If you want to measure inflammatory markers after hyperacute exposure to toxin, measure C4a, which changes within a day.
           3. Cytokines can cross the blood-brain barrier to bind to a [Leptin](#Leptin) receptor, which lowers MSH transcription…

Leptin rises with acute receptor resistance on day 2

MMP9 increases on day 3

* + - 1. Fixing cytokines helped many but not all; what else was there?
      2. Not all people had cytokine excess
      3. VCS helped a lot, but some stayed ill *despite corrected* VCS
    1. 5-year follow-up of Pfiesteria Exposed
       1. Triple-matched controls
       2. Despite symptom-improvement, there was a…
       3. Dramatic increase in death and disability within five years
       4. VCS/MMP9/VEGF (Vascular Endothelial Growth Factor)/ADH/Osmolality were all OK
          1. VEGF released in response to capillary hypoperfusion🡪reduced oxygen delivery to tissues
          2. Increasing VEGF will bring about greater oxygen delivery after cytokine-induced capillary hypoperfusion
          3. New blood vessel formation also happens with increased VEGF
          4. Remember that cancer is an obligate aerobe; it uses sugar for energy, thus requiring a lot of tissue oxygen delivery…
          5. Increasing VEGF could increase cancer growth
          6. VEGF inhibitors are key oncologic interventions
          7. Low VEGF is quite common in biotoxic patients

They have capillary hypoperfusion

They’re not delivering more oxygen due to rising VEGF when they should be

They’re functionally acting like they were exposed to a chemotherapeutic agent for cancer

Fumagilin, made by Aspergillus fumagotus inhibits endothelial growth

Low VEGF can be fixed by Actos/no amylose diet

Remember, Actos lowers Leptin, if Leptin<7 then use

Omega-3 fatty acids at high doses

2.4 gm. EPA/d

1.8 gm. DHA/d

* + - 1. What was missed?
  1. Enter C3a, C4a from work by Dr. Giclas
     1. C3a and C4a are produced from cleavage/activation of Complement;
     2. C4 activation is accomplished by MASP-2 (Mannose-binding elected associated serum protease)
        1. MASP-2 is activated by
           1. Ficolins
           2. Acetylated environmental compounds

This is similar to what Benomyl did

* + - * 1. The toxicity seems to actually be coming from C4a

To aggravate this situation, MASP-2 can actually auto-activate or turn itself on.

* + - * 1. So use of Benomyl in 1974 to prevent fungal growth in paint, created new classes of mutant fungi
        2. Generally speaking, without a ficolin or acetylated environmental compounds, MASP-2 doesn’t get turned on.

Thus, C4a won’t be elevated

* + - 1. Stunning!
  1. Biotoxins
     1. *Very* small molecules; ionophores
        1. Ionophores are able to move from cell to cell
     2. Inflammagens bind to receptors
        1. Toll; mannose, ficolins, C-linked lectins
     3. Predictable inflammatory results
     4. Direct measurement of biotoxins in blood is not helpful
        1. The chance of finding it in the blood is about zero
        2. The chance of finding it on it’s receptor is much higher
        3. The disassociation concentration for Ciguatoxin is about 1X10-14; it’s highly bound to it’s receptor; a blood test won’t help
        4. How can Cholestyramine remove Ciguatoxin?
           1. The answer is that the disassociation constant is not zero.
           2. Although highly bound, it will eventually migrate off of the receptor so that it can be bound in the gut and removed.
           3. Ciguatera responds much more slowly than Pfiesteria or mold toxins, which have much lower disassociation constants.
     5. **Examples of biotoxins;**

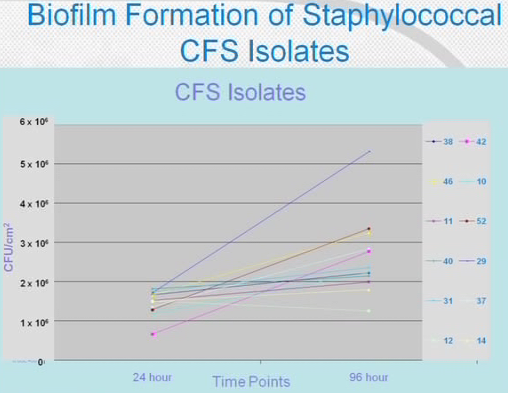
|  |  |  |  |
| --- | --- | --- | --- |
| **Agent** | **LD50** | **Molecular Wt.** | **Source** |
| Botulinum | 0.001 | 150,000 | Bacterium |
| Shiga Toxin | 0.002 | 55,000 | Bacterium |
| Diphtheria Toxin | 0.10 | 62,000 | Bacterium |
| Maitotoxin | 0.10 | 3,400 | Marine Dinoflagellate |
| Ciguatoxin | 0.40 | 1,000 | Fish/marine Dinoflagellate |
| Batrachotoxin | 2.0 | 539 | Arrow-Poison Frog |
| Ricin | 3.0 | 64,000 | Castor Bean |
| Conotoxin | 5.0 | 1,500 | Cone Snail |
| Tetrodotoxin | 8.0 | 319 | Puffer fish |
| αTityustoxin | 9.0 | 8.000 | Scorpion |
| Microcystin | 50.0 | 994 | Blue-Green Algae |
| Sarin | 100.0 | 140 | Chemical Agent |
| Aconntine | 100.0 | 647 | Plant (Monkshood) |
| T-2 Toxin | 1,210.0 | 466 | Fungal Mycotoxin |

* 1. What can be fixed about C3a elevations?
     1. C3a is generated when C4a & C2a are made by the activation of MASP-2; splitting C4 & C2 together creates C4b and C2a that activate C3 *if there is a bacterial membrane present*
     2. C3a presence indicates that bacterial membranes are still present inside blood
     3. C3a increases within 12 hours of a tick bite in people who go on to develop Lyme disease
     4. If HLA is Lyme-susceptible, the patient will probably need more than just 3 weeks of antibiotics.
        1. If not HLA susceptible, then resolution of elevated C3a, C4a and VCS should occur without further intervention.
     5. If, after 3 weeks of antibiotics, there is still sero-evidence of infection, then it’s time to start therapy for CIRS.
        1. Baseline CIRS serology is drawn before giving antibiotics for Lyme.
        2. If dealing with a new tick-bite patient, the window for inflammatory change is 96 hours, after 96 hours there should be evidence of inflammation if the tick was infected
           1. VCS is a quick/easy test to use before drawing labs; if it’s normal 96 or more hours after tick bite, there was probably no Borrelia
        3. After three weeks of antibiotics, if C3a & C4a are still elevated, a month of Cholestyramine and Actos are given, and then after a week of no medications, repeat C3a and C4a are rechecked.
           1. If C3a is stable with C4a increasing, then the patient has had a concurrent mold toxin exposure.
           2. Labs won’t be available overnight

Check their VCS

Check their symptom level; are they improving?

* + - 1. If C3a & C4a are stable, repeat them in a month
         1. If there are still live Lyme spirochetes (Borrelia burgdorferi) the C3a (membranes present) and C4a (causing inflammation) will rise within a month.
    1. If live organisms are present after 3 weeks of oral antibiotics, it may be time to switch to IV antibiotic therapy
       1. If C3a is still elevated after three weeks of antibiotics, then…
       2. High dose statins had some literature support
          1. Some of the beneficial effect of statins may be due to lowering C3a
       3. Such high doses caused outrageous muscle cramping and rhambdomyolysis
       4. Statins lower ubiquinone and ubiquinol (CoQ10)
       5. Replenishment of CoQ10 with 150 mg/d improves tolerability of statins
          1. Pre-treat with CoQ10 for a few weeks prior to starting statins
       6. C3a was no longer a big problem
  1. C4a Appears as an available lab test in June 2005
  2. MR Spectroscopy allows measurement of;
     1. N-Acetyl aspartate; a marker of CNS white matter disease
        1. Creatine as a control & cell mass measure
     2. Acetyl choline
     3. Myoinosotol; indicates glial cell injury
     4. Lactate
     5. Mold Warriors was outdated within 2 months of publication
     6. Correcting existing illness helps
     7. High C4a is correlated with CNS capillary hypoperfusion
        1. Lactate;
        2. Glutamate (excitatory) to Glutamine (inhibitory) ratio (excite/inhibit) (ate/ine)
        3. With reduced capillary perfusion comes reduced mitochondrial activity (& aerobic respiration)🡪 increase lactate production from glycolysis.
        4. Brain fog is associated with increased lactate and suppression of the Glutamate/Glutamine ratio (more inhibition than excitation)
     8. Lowering C4a with erythropoietin corrected lactate and G/G
        1. Excessive clotting happens with head and neck cancer
        2. HIV is a heavily cytokine influenced disease
        3. Low doses of erythropoietin are used;
           1. Erythropoietin causes tissue remodeling/repair
           2. 8,000 units erythropoietin SQ Monday and Thursday for a total of 5 doses, (1 40,000 unit vial)
           3. Higher doses of erythropoietin once/week show no benefit due to its short half-life of 1.5 days.
           4. Repeat MR Spectroscopy after erythropoietin
           5. Informed consent is signed before erythropoietin therapy. It’s just “off-label” use of the drug.
        4. Cognitive effects disappeared
     9. This is Lab-Intensive Medicine;
        1. Review and copy morning labs
        2. Prepare data sets constantly
        3. Patterns emerge; look at the correlations that come from reading trends and graphs
        4. Picking out lab errors is easy
        5. HLA DQ3 versus HLA DQ7 in 2004; LabCorp changed their reporting system of these two haplotypes
     10. Being a lab-jockey can show flaws in medical dogma
         1. Celiac disease association with HLA DQ2 (and 8 a little bit) right?
         2. Wrong! It’s associated with 17-2-52 A, B, C and then 7-2-53
         3. Linkage disequilibrium
         4. Mold illness is too; how many AGA (+) people were moldy or Lyme or CFS? Just about all of them)
  3. Sure enough, MMP9 is a problem
     1. Esoterix set up an assay for Dr. Shoemaker only
     2. The only person in the US with MMP9 data was Dr. Shoemaker
     3. Only he knew cases and controls
     4. Esoterix lumped all values together to create a “normal” range which was garbage
     5. Quest agreed to do the work properly
     6. MMP9 must be drawn in a clot or SST tube
        1. Tube is not allowed to set up at room temperature which means macrophage activity is not going to be stopped by room temperature clotting.
        2. MMP9 is generated by macrophages and endothelial cells
        3. If you don’t control how the specimen is handled, your MMP9 levels will double and triple at room temperature in as little as 30 minutes.
        4. The specimen must be drawn into a cold tube, immediately centrifuged and refrigerated.
     7. Only in 2011 is the MMP9 normal range problem corrected;
        1. LabCorp purchased Esoterix in 2004
        2. Continued to use the normal range of <984
        3. Would not listen to logic
        4. Quest does the MMP9 levels
           1. Normal is <332
        5. Quest won’t do this for other physicians
  4. MSH
     1. ALPCO kit done by LabCorp
     2. Normal range is 35-81 pg/ml
     3. Suddenly on 9/26/06 normal range is 0-40
        1. “0” is never a normal range for these metabolic regulators
     4. The only change was a lawsuit in Maryland 8/15/06 where low MSH was of key importance and the insurance company paid out a lot of money
     5. Now <35 is a “critical value”
     6. LabCorp “threw Dr. S a bone”
        1. They now label MSH <35 as a panic value requiring immediate notification of ordering provider
        2. They formerly ran the MSH Friday afternoons, necessitating weekend calls
        3. Now they run the tests Friday mornings, fax the result and have an undisturbed weekend
  5. Microbiology leads the way to next; Biofilm
     1. What is this biofilm?
        1. Bacteria differentiate inside the biofilm
        2. Standard cultures of the nares will show the faster growing organisms, not the organisms in the biofilm, which grow slower. The faster organisms are reported in 48 hours
     2. You must use an *API Staph Isolate* to get the biofilm forming Coagulase (-) Staph <https://www.dxos.com/mold-illness-testing/>
        1. Swab has a pink-red top
        2. Insert swab as deep into the nare as possible, beyond the turbinates, leave the swab at the back of the nasopharynx for 5 seconds
        3. Most MARCoNS (+) patients will want a second culture to prove eradication.
        4. MARCoNS (+)/MSH deficient patients will get very little improvement with Cholestyramine alone if the infection isn’t also treated.
        5. Knock out toxin carriage with Cholestyramine, then MARCoNS with BEG; follow with VCS to document progress each step of the way.
     3. Why do these funny staphs make an exotoxin that splits MSH?
        1. Coagulase Negative Staph develop best in an MSH deficient patient
        2. The staph must be eliminated after the first month of Cholestyramine
        3. Use BEG spray; Bactroban, EDTA & Gentamycin from [Hopkinton Compounding Pharmacy](http://www.rxandhealth.com)
        4. These MARCoNS in MSH deficient patients also lower the T-Regulatory lymphocytes
           1. This is a case of commensals affecting the human body’s immune regulation
           2. Who knows what is also going on in the gut with a billion anaerobes for every 10 aerobes?
     4. What does hemolysin do?
        1. If the biofilm formers are true commensals, there must be permissive host factor right?
        2. Guess what?
        3. Staph biofilms also lower CD4+, CD25+ too
        4. The whole idea of commensals altering host response isn’t confined to nasal staphs
        5. Look at the GI tract
        6. Consider; could autism be part of the result of this?
           1. They can be colonized by multiple unusual Clostridia species
        7. Clostridia boltii?
     5. Where else is MARCoNS? Dr. Kulacz
        1. Culture of deep nasal aerobic space
        2. Pulled a tooth the next day
        3. Culture of both sites yielded the same organism
        4. Nothing happened with treatment until the VCS improved
        5. Then Dennis Katz invents the BEG spray
     6. BEG Spray (Bactroban/EDTA/Gentamycin from Hopkinton Compounding)
        1. Proprietary formula
        2. Look at all of the EDTA in baby shampoo
        3. Used with oral Rifampin; beware, GI & red staining (do NOT use with Coumadin)
        4. Reduced carriage after Rx to <5%
     7. Rifampin Resistance
        1. Bartonella is over-diagnosed
           1. Quinolones are probably overused
        2. Rifampin resistant organisms are very unusual in the wild; are tough to eradicate
           1. Excess use of Rifampin for putative Bartonella can lead to Rifampin resistance in MARCoNS
        3. Crummy diagnosis of Bartonella leads to injury onto which more antibiotics are dumped
        4. We need a good assay for Bartonella
           1. Nasal smears are inadequate to Dx Bartonella
     8. Just do the nasal culture!
        1. Is the $50 cost of the nasal culture worth doing if you might spend $20K for Rocephin
        2. API-Staph is needed <https://www.dxos.com/mold-illness-testing/>
           1. Remember, biofilm forming organisms grow very slowly
           2. They’re outgrown in routine cultures
        3. Best investment anyone can make in low patients with low MSH
        4. If [API Staph](https://www.dxos.com/mold-illness-testing/) done for a Lyme patient given antibiotics, the antibiotics may produce a Herxenheimer die-off reaction
           1. The die-off reaction does not mean that MARCoNS were eliminated
           2. MMP9 & VCS will give information on whether MARCoNS is still present
           3. Biofilm formation of Staph CFS Isolates (image below)



* + - 1. The more biofilm is present, the worse the disease is
  1. [VEGF](#VEGF)
     1. Vascular Endothelial Growth Factor
     2. Responsive to Hypoxia Inducible Factor [(HIF);](#HIF) feedback from TGF β-1
        1. VEGF rises quickly with hypoxia
        2. In Re-exposure protocol patients, VEGF will also rise quickly initially, but as TGF β-1 is made, the VEGF will decrease
        3. On Day 1 of a re-exposure protocol of a mold patient into a building, it rises, then declines by day 3 when TGF β-1 increases as a feedback interaction from TGF β-1 on VEGF
     3. Increases oxygen and new blood vessel formation
        1. Jonah Folkman and anti-angiogenesis knew about VEGF
        2. Blockade of VEGF is a big deal in onco-chemotherapy
           1. It’s most effective at VEGF (+) receptor tumors
     4. But *low* VEGF is the norm in the worst biotoxin patients
        1. There will be some *“U-shaped” Skew*, but…
           1. Normal range is 31-86
           2. <31 with biotoxin/CIRS patients
           3. Few normal range patients
           4. Some patients are >86
     5. LabCorp “normal” is 0-115 which is meaningless
     6. Quest has ranges similar to LabCorp; unreliable.
     7. *Low VEGF means cell-based starvation.*
     8. So why are cancer rates lower in CIRS patients than in the general population?
        1. Is it VEGF related?
        2. Remember, WDB’s have multiple carcinogens!
           1. Mycotoxins are often carcinogenic
     9. Remember; do not ignore low VEGF!
        1. The answer must account for the initial rise in VEGF followed by the crash, as we will see in SAIIE.
     10. Measure VEGF, Normal range 31-86; don’t ignore low VEGF!
         1. The biology of VEGF is complex!
            1. VEGF is down-regulated by TGF β-1
            2. Actos on Amylose-Free diet and Omega-3’s are key to raising VEGF
     11. Capillary hypoperfusion
         1. Bottom line is decreased delivery of nutrients and oxygen into capillary beds
         2. ABG’s won’t help, venous gasses don’t have any academic basis in these illnesses
         3. Use VO2max from Pulmonary stress testing (PST).
         4. Use lactate in MR spectroscopy (which is better than PST)
     12. VO2max
         1. Disability examiners frequently use this measurement
         2. Should be >35 in healthy younger people; nomograms are available
         3. 12 ml/kg/min is Stage 4 CHF
         4. Conversely, training to raise VO2max that doesn’t go beyond the anaerobic threshold works in biotoxin patients.
         5. Pulmonary Stress Testing (PST) determining the anaerobic threshold and VO2max is a great way to get disability status for patients and know the reality of that subjective complaint of chronic fatiguing illnesses
         6. Erythropoietin and VIP will increase VO2max
     13. Raising the VO2max shows benefit;
         1. Correcting VEGF must happen
         2. Anaerobic threshold is measured
         3. At exercises; start low, go slow
         4. Must do defined exercise EVERY DAY!
         5. Bike, treadmill, work up to 15 minutes
         6. Add floor exercises, build up to 15 minutes; then free weights
         7. Go back to first defined work
         8. Increase sequentially on all parameters
         9. This regimen will dramatically increase exercise capacity.
     14. Post-exertional malaise [(Mitochondrial Evaluation)](http://www.tequestafamilypractice.com/articles/MCSOverview.htm#mitochondrial)
         1. Measure VO2max with PST
            1. It will be low
         2. What about glycogen in exercise?
            1. Remarkably inefficient glucose oxidation
         3. No oxygen, no efficiency
            1. This will rule out mitochondrial illness!
            2. With mitochondrial illness, metabolism will be anaerobic producing pyruvate and lactate.
            3. Capillary hypoperfusion also produces pyruvate and lactate with the anaerobic metabolism
     15. Fat storage; after glucose/glycogen are exhausted, fat is used next]
         1. Fat oxidation requires oxygen
         2. Look at Leptin values; there may be Leptin resistance caused by the cytokine activity of CIR, if so, Leptin values will rise
         3. Since fat oxidation requires oxygen, the only thing left to burn for energy is…
     16. Protein burning after fat supply is exhausted ([Amino Acid Profile](http://www.tequestafamilypractice.com/articles/MCSOverview.htm#AminoAcid))
         1. Alanine and Glutamine the first amino acids to convert to glucose
         2. Remember; exceeding the anaerobic threshold in the absence of carbohydrate leaves only one option; protein catabolism/oxidation for energy.
         3. With Leptin resistance, fat weight is gained due to the high Leptin values as lean body mass decreases.
  2. VIP is one of the newest players in the CIRS realm (usually low in CIRS)
     1. 26 amino acid neuropeptide in the secretin family
     2. Neuromodulatory and immunomodulatory
     3. Also affects hormones/endocrine system
     4. CIRS patients have a more profound VIP deficiency than their MSH deficiency
     5. Elevated VIP at baseline is possible but rare
        1. Requires an octreotide scan looking for a GI VIP-oma (very rare)
     6. Neuropeptides that interact with each other include;
        1. Secretin with VIP
        2. Vasopressin with MSH
        3. VIP has a lot of literature describing what it does
           1. Has a strong effect of reducing pulmonary artery systolic pressure
           2. Binds to membrane receptors to raise intracellular cyclic AMP (cAMP)
           3. Down-regulates cytokines
           4. With exercise, it reduces pressure between the right side of the heart and the lung.

Increases Right then Left ventricular stroke volume by doing so.

Thus increasing exercise tolerance

* + - * 1. If Right ventricular stroke volume is reduced or the work required to maintain it is increased, then Left ventricular output will also drop, decreasing Cardiac Output (CO) is (Stroke Volume X Heart Rate)

We depend on venous return to supply Left Atrium to Left Ventricle to enhance stroke volume, which we cannot attain due to increased pulmonary artery pressure, then

* + - * 1. Heart rate must increase to increase the CO/CI producing
        2. Tachycardia, palpitations, SOBOE, tachyarrhythmia’s

Above could be due to pulmonary disease, COPD, Asthma, Fibrosis

It may be acquired pulmonary hypertension

* + - 1. Dr. Shoemaker did a study on what VIP might be able to do for Pulmonary Hypertension with a clinical trial;
         1. Subjects had low VIP as entry criteria with Hx of elevated C4a & elevated TGF β-1 and a rise >8 Torr Pulmonary Artery Pressure during cardiac stress testing/exercise
         2. 50 mcg dose of VIP was given to subjects qid
         3. NOTE; VIP must be kept refrigerated stored upright in nasal delivery bottle
         4. At the end of a month of qid VIP, repeat lab parameters & pulmonary stress testing was done🡪benefit was provided by qid dosing
         5. Bid dosing was then tried; lab & PA pressures🡪all was OK but

Early on there were a number of subjects who felt better on qid than on bid dosing

This cohort was not decreased to qd dosing but the others were

* + - * 1. All subjects were followed for one year then re-tested
        2. Most people, after 6 months can tolerate a reduced dose of VIP from qid to bid, sometimes to qd
        3. This VIP intranasal protocol has essentially cured a large group of chronic fatigue patients.
      1. FDA has designated VIP for treatment of Pulm Htn (other uses are off-label)
    1. Remember, if using VIP then sustaining exposure to toxin/WDB etc., everything “goes back to square one”.
       1. The response will be truncated and shortened however after recovery from symptoms by a course of VIP.
       2. Patients will tolerate longer periods of exposure as well.
    2. VIP down-regulates MASP-2 (C4 activator to C4a)
    3. VIP restores balance of Vitamin D3
    4. VIP down-regulates aromatase which breaks down testosterone among other hormones
    5. VIP up-regulates (increases low levels of) VEGF
       1. If Actos or fish oil/omega-3 doesn’t work, VIP will correct
    6. Warning Re; VIP may cause Lipase to increase a bit; measure baseline and monthly X 3 VO2max
    7. VIP’s main effect immediately is endorphin mediated…
       1. Typically within 5 minutes of first dose patients can take a deeper breath
       2. Joint symptoms @ baseline; tight clenched hands will typically open and relax on VIP
       3. Immediate pain relief is a big deal and much appreciated
       4. Cognitive issues respond more slowly
          1. Draw blood at baseline (Lipase, VEGF, C4a, TGF β-1), give VIP, repeat draw (VEGF, C4a, TGF β-1) in 15 minutes
          2. If there is a sudden increase in TGF β-1, there has probably been recent exposure to WDB with ongoing mycotoxin exposure.
    8. Followed by lowering Pulmonary Artery Systolic Pressure (PASP) in exercise
  1. PA Systolic Pressure (PASP) and VIP
     1. 50-mcg qid corrects paradoxical rise in PASP in exercise in days, not weeks, with durable effects with titration to bid and over time, discontinuation!
     2. So many people are not diagnosed with acquired Pulmonary Hypertension (PASP elevations) even if they have a stress echo, it MUST precisely *measure* degree of Tricuspid Regurgitation!
        1. Estimated PASP is; the square of (TRX4) + RV pressure calculated from the Echocardiogram recording. Calculations are done on the digital reading from the recording.
     3. Don’t accept “Normal” on stress-echo report!
  2. Measure PASP with exercise (increased SOB with exertion)
     1. “Looks like asthma” but it isn’t
     2. PASP should not rise more than 8 Torr with exercise
     3. Can cause palpitations and SOB
     4. Won’t improve with beta-2 agonists (albuterol etc.)
     5. Don’t forget EMT and TGF β-1
  3. In the face of VIP deficiency, TGF β-1 may increase with exercise
     1. TGF β-1 causes cells to transform/tissue remodeling (TRANSFORMING GROWTH factor…) with fibrotic changes in organs…
     2. Remodeling occurs in the heart, CNS, liver, lung
        1. Fibrotic changes
        2. Seems to increase alteration of columnar epithelial cells of the airway to fibroblasts
           1. Therapy with agents that reduce TGF β-1 such as VIP will cause IMPROVEMENT in organ function, structure/histology
  4. Other VIP Effects;
     1. Immunoregulatory; this is a Neuro-Immune link
     2. Drives up CD4 + CD25 + FoxP3
        1. CD4+, CD25+ are regulatory T-Cells detected on a flow-cytometry assay
           1. Either CD4+, or CD25+ don’t give useful information
           2. The COMBINATION of CD4+ AND CD25+ provides the useful data
        2. FoxP3 is a nuclear replication factor that provides greater sensitivity than CD4+ and CD25+
     3. This demonstrates the link from neuropeptides to humoral factors to T-cell physiology
        1. Role of down-regulation of TGF β-1 has no obvious upper limit in its application.
     4. Low TGF β-1in post-Lyme patients treatment with antibiotics
        1. If NOT HLA-susceptible the CD4/CD25’s come back up to normal
        2. HLA-Susceptible pt’s won’t get that effect with antibiotics
           1. Biotoxin/CIRS therapy will bring the CD4/CD25’s back from ~6 which is low up to about 17 (18 is normal)
           2. Adding VIP will drive the number into the mid-20’s
  5. Downsides to VIP
     1. It’s not cheap
     2. Must be refrigerated (OK at room temperature for ~8 hours)
     3. Not FDA approved, is FDA designated
     4. No Benefit If;
        1. (+) VCS; it’s necessary to clear out the toxin effect before starting VIP
        2. ERMI >2; DO ERMI testing, don’t accept worthless air testing

[(a) ERMI does not account for non-mold inflammagens including VOC’s, endotoxins, Actinomycetes, glucans, glycoproteins & other noxious incitants.](http://www.slideshare.net/keithberndtson/mold-toxicity-syndrome-cirs)

* + - 1. (+) Nasal MARCoNS (do the test from Cambridge labs!)
  1. Is VIP Too good to be true?
     1. Reduces SOB/Cognitive problems improve or resolve
     2. Reduces joint stiffness in ~10 minutes (causes endorphin release)
     3. Improves exercise tolerance
        1. First noted within 2 hours
        2. By 2 days, dramatic effects
     4. Global improvement in all modalities
     5. Downsides; as above, will increase circulating lipase;
        1. (Maintain index of suspicion if pancreatic/biliary complaints)
     6. VIP is safe, basically impossible to overdose
     7. Excellent record to date on over 400 patients
     8. Easy to use, portable, effective!
        1. Finally available by Rx
        2. Just about every Chronic Fatigue Syndrome patient is deficient in VIP
           1. As soon as word gets out, LOOK OUT!
           2. Concern; people will leap to its use without recognition of what makes it *not* work.
  2. What makes VIP NOT work?
     1. ERMI >2 at home/work/school
     2. ERMI interpretation; <http://www.survivingmold.com/diagnosis/hertsmi-2>
     3. VCS still positive
     4. Untreated
        1. MARCoNS
        2. MMP9
        3. PAI-1 (Plasminogen Activator Inhibitor-1)
        4. High Leptin
        5. High C3a
        6. High C4a
        7. High TGF β-1
     5. Ongoing exposure
  3. TGF β-1 Generates TH17 cells, turns on T-regulatory Cells, made by T-effector cells
     1. Will have its own section
     2. Is the key advancement in assessment of CIRS
        1. Lung symptoms? Ask Re TGF β-1
        2. Neuro problems/Eg resting tremor? Ask Re TGF β-1
        3. Autoimmune? Ask Re TGF β-1
        4. Learning disability? Ask Re TGF β-1
        5. MS? Ask Re TGF β-1
        6. TM? Ask Re TGF β-1
     3. First found to have increased tissue effect in those with mutated fibrillin-1
     4. Then the switch to plasma measures
     5. TGF β-1 normal is <2,380; >5,000 start to worry
     6. >10,000 essentially guarantee restrictive lung disease, tremor, cognitive issues and joint problems.
     7. Must be done only on double-spun plasma drawn in chilled tubes as platelet-poor plasma. Need as few platelets as possible
     8. If result >40,000 the specimen was not properly handled
        1. Always have a 2nd specimen saved
     9. Diagnostic Laboratory Medicine Bedford MA <https://www.dxos.com/mold-illness-testing/>
  4. MR Spectroscopy
     1. Requires a 3 Tesla coil; single voxel
     2. Examines
        1. Frontal lobes (memory)
        2. Hippocampi (memory and spatial navigation)
     3. Measure the same spots/same compounds!
     4. High lactate; >1.29 is to high (problematic)
     5. Ratio of Glutamate/Glutamine (G/G); <2.19 is to low (problematic)
     6. Change in cognition is a tip-off
     7. Therapy is aimed at lowering the elevated C4a, causing reversal of high lactate also reverses suppressed G/G
     8. Voila🡪reversal of cognitive issues!
     9. Key concept is that *cellular neuronal mechanisms are not permanently injured!*
  5. T-Regulatory Lymphocytes
     1. Thymic derived cells don’t play much of a role in CIRS
     2. These are “Induced” T-lymphocytes due to action of high levels of TGF β-1
        1. With active tissue inflammation the three populations of cells below will be hydrolyzed in the inflamed tissues to release T-effector cells which are pathogenic and in turn produce more TGF β-1
        2. CD4+, CD25+, FoxP3 cells
        3. Untreated 6.2; treated 18.7
        4. Controls 17.8; relapse 5.4
        5. Re-treated 19; VIP 24!
     3. But FoxP3 unmeasured although LabCorp is setting up an assay for them.
     4. Conversion to pathogenic T-cells in tissue (like Einstein’s unknown nuclear factors!)

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1. **2011; Genomics time**
   1. Examining how to stratify patients and controls by differential gene activity
      1. Genetic “Fingerprint” is now available for;
         1. Ciguatera
         2. Post-Lyme
         3. WDB pt’s with mycotoxins
      2. Chronic fatigue work is ongoing
         1. 500 genes (out of the 40,000 in the human genome) have been selected for evaluation for CFS etiologies
      3. Add proteomics
      4. Add differential diagnosis, and then try to add in…
      5. Epigenetics
      6. We’re still back to the essentials of any ecosystem; at 30,000 feet
   2. [www.mycometrics.com](http://www.mycometrics.com) for ERMI testing; $300.00🡪2 samples/bldg. analyzed
      1. Looks at 9 different fungal types
         1. Wet-wet 80-100% saturation
            1. Ketonium
            2. Stachybotrus
         2. Medium Wet-wet 70-80% saturation
            1. Aspergillus

Fumagotus

Niger

Versicolor

Penicilloides

Ochraceus

* + - 1. Dry-wet 60-70% saturation, heating duct environments
         1. Wallemia
         2. Trichoderma
    1. Any ERMI >2 with MSH <35 in a susceptible haplotype🡪 CIRS

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1. **Treatment of Chronic Inflammatory Response Syndrome**
   1. Remove from exposure!
      1. There is no “safe” threshold for exposure; any exposure is bad!
      2. This is a *host* response, not a *dose* response
      3. Remove mycotoxic exposure as above
         1. Big issue with public schools and many other bldgs.
      4. We’re assuming that there is no Lyme exposure
      5. We’re also assuming that there is no Ciguatera, Pfiesteria etc. exposures
   2. **Cholestyramine or Welchol** are the only therapeutic choices
      1. Pediatric dose 60 mg/kg tid
      2. Colestid will not work
      3. Activated charcoal doesn’t seem to work.
      4. Take Cholestyramine at least 30 minutes before meal with extra fluid to wash it out of the stomach and into the duodenum, it needs to be by the sphincter of Oddi for maximum effect.
         1. Dose qid with meals
         2. No benefit from doubling the dose
         3. No benefit from more frequent dosing
      5. Welchol has a much gentler/better side effect profile than Cholestyramine.
         1. Welchol has about 20% the efficacy of Cholestyramine due to fewer quaternium ammonium binding sites for the bile acids
         2. Will probably take >2 months to get the effect of 2 months of Cholestyramine therapy
         3. Dosed 2 tabs tid with food
      6. It’s OK to take Cholestyramine AM & PM and two doses of Welchol during the day for the sake of convenience.
      7. Use VCS to follow progression and document how well that the exposures/toxins that cause cytokine release & capillary hypoperfusion have been removed/resolved
      8. Continue the above drugs as long as the VCS is positive
      9. When the VCS becomes negative, cut back on or stop the Cholestyramine or Welchol
         1. Provided there are no new exposures or re-exposures!
         2. If there is a new exposure with MSH <35, it’s back to “square one”.
         3. If on VIP patient won’t get as sick as if not on VIP; will tolerate exposure better but will still be susceptible.
            1. Non-VIP patients will “get sicker quicker” after new/re-exposure
            2. Even with continued exposure, Cholestyramine etc. can help lower toxin load and delay maximum illness in CIRS.
            3. The C4a activating system was “primed” by the first encounter
            4. It now responds quicker (in absence of VIP)
         4. If VCS does not improve or normalize after a couple of months of therapy, there must be other sources of exposure.
            1. If there is low MSH with high C4a (especially after C4a goes >20,000), it takes about an hour of exposure to reverse the effect of two weeks of Cholestyramine.
            2. If the original exposure was Lyme, Cholestyramine is started, then there’s exposure to a WDB, and then the patient will relapse back to square one requiring re-initiation of therapy starting with exposure avoidance… (If the mistaken assumption is that this is more Lyme without doing ERMI in all exposure environments (home, work, school, church etc.) then there will be no improvement.
      10. After a month of treatment, if VCS normalizes, you need the result of the deep nasal API-Staph culture (which should be done at the initial visit so that the results will be available at the follow-up).
   3. MRCoNS
      1. To treat API-staph (+) deep nasal cultures <https://www.dxos.com/mold-illness-testing/>
      2. If positive, use BEG Spray each nostril tid (from Hopkinton [www.rxandhealth.com](http://www.rxandhealth.com)) with Rifampin #2 of the 300 mg tabs q AM
         1. If unable to tolerate Rifampin
            1. Maybe wrongly treated for presumed Bartonella
      3. Higher-dose VIP is the only other option with BEG but no Rifampin
      4. Consider 2 sprays/nostril tid as “double strength” BEG as another option
   4. Antigliadin antibodies
      1. Gluten is generally more of a problem for children than adults
      2. That doesn’t always hold true for CIRS patients
      3. Dr. Shoemaker follows anti-gliadin antibodies; IgM, IgG and IgA in blood, no salivary testing
      4. In the presence of MSH deficiency, TGF β-1, T-regulatory cell dysfunction, then there are probably ongoing autoimmune problems.
         1. Gliadin happens to be the most common of the autoimmune triggers.
         2. Patient must abstain from gluten for 3 months before the test will convert to negative.
         3. [www.celiac.com](http://www.celiac.com) is a great resource for dealing with gluten-free diets.
      5. If there are no symptoms of celiac disease but the antibodies test (+), then IgA Tissue Transglutamase profile is sent off for evaluation
         1. If the IgA TTG profile is negative, it denotes that this is not celiac disease; it’s merely a case of low MSH autoimmune problems.
      6. With 3 months of a gluten-free diet, the vast majority of patients will convert to IgG/IgA negative anti-gliadin antibody status.
         1. Then let them eat gluten to see if they convert back to (+), if they do convert…
         2. They probably are gluten sensitive and should abstain from gluten forever.
   5. MMP9
      1. MMP9/ADH-Osm/Androgens can all be lumped together for the sake of therapy
         1. When they occur, they usually occur in this cluster, all together
      2. Will usually fall back to normal with CIRS therapy
      3. If it doesn’t, then Actos/low amylose diet and Omega-3’s will help lower it
      4. High levels of MMP9 can cause problems
         1. Levels will be <500 in control patients
         2. CIRS patients will typically be ~/>900
   6. ADH/Osmolality
      1. ADH/Osmolality will be dysregulated in about 80% of CIRS patients
      2. By correcting exposure, binding toxins with Cholestyramine/Welchol and treating MARCoNS, most of the ADH/Osm problems will resolve
      3. Look for polydypsia/polyuria/static shocks
         1. ADH in it’s range should match what the Osmolality is in its range
         2. If Osm normal is 280-300 with a patient result of 295, then expect the ADH to be about 12 if the normal range is 1.5-13.3
         3. Formal calculations can be done but are probably not necessary since it will typically auto-correct with initiation of CIRS therapy
         4. If the ADH remains low for a given osmolality, the patient may be drinking enough to keep their osmolality down, but they can’t drink enough to keep their ADH down.
         5. Consider using DDAVP to increase the urine osmolality but it will cause water-retention/weight gain due to decreased serum osmolality.
         6. If ADH is 0.8, the Osm should be around 280, consideration can be given to use of DDAVP, but it will probably correct with CIRS treatment.
            1. DDAVP is best dosed at night every other night for 5 nights, then re-measure serum osmolality and serum Na
            2. DDAVP can cause significant hyponatremia
            3. Then advance to daily dosing (hs) and recheck serum osm and Na
            4. Rarely does a patient need more than two doses of DDAVP/d
            5. Expect to see reduction of thirst, urination, static shocks and headache
   7. Androgens
      1. Inflammation can cause up-regulation of Aromatase
      2. Use of aromatase inhibitors with a low-MSH patient, they will cause them to deteriorate to tenfold worse than before the inhibitor was started.
      3. Do not use aromatase inhibitors in patients with MSH<35
      4. Consider use of DHEA as an upstream androgen replenisher, which can increase testosterone levels.
      5. Monitor Estrone/Estradiol/Estriol to ensure the estrogen levels are not increasing with the additional DHEA.
      6. Use of VIP will stabilize aromatase
      7. Testosterone/Estrogen ratio’s can be helpful to document excess aromatase effects
   8. C3a (increases when bacterial membranes are in the vasculature)
      1. Correction of any underlying Lyme is important
      2. C3a does not increase in Bartonella patients, probably because there are not many Bartonella cell membranes within blood vessels
      3. C3a elevations can be spectacular in people with cardiovascular issues
      4. C3a elevations are common with Raynaud’s syndrome as well, correction will help the Raynaud’s
   9. C4a
      1. Elevations are far more common than C3a elevations
      2. Erythropoietin lowers C4a
      3. Very good indicator for mycotoxins.
      4. Erythropoietin Protocol; Baseline TGF β-1, C4a, D-Dimer, CBC
         1. If Hb goes >16.5, it’s to high (FDA doesn’t want it >10)
         2. Ensure informed consent is signed
         3. Record the Lot Number of the erythropoietin that is used; there have been recalls
         4. Erythropoietin antibody formation was a complication that occurred with one brand of the product that has been removed from the market.
   10. TGF β-1
       1. Humoral marker for immunity
       2. Responds to Losartan (Cozaar) and responds even better to Losartan degradation product; exp3179
          1. Exp3179 doesn’t change BP but does reduce TGF β-1
          2. Unfortunately, a lot of CIRS patients are orthostatic; Losartan wouldn’t be a good idea due to that problem…
       3. Losartan 12.5-50 mg qd to bid causes conversion of autoimmune problems as TGF β-1 is lowered.
          1. This effect was probably more to the Losartan effect on T-regulatory cells than TGF β-1 alone
          2. But if there are low T-reg cells and the TGF β-1 remains elevated, give a trial of Losartan before trial of VIP and then, do what you have to do to give them VIP.
   11. VIP
       1. 50 mcg dose of VIP was given to subjects qid
       2. NOTE; VIP must be kept refrigerated stored upright in nasal delivery bottle
       3. Down-regulates MASP-2 (C4 activator to C4a see # XII U 1)
       4. Restores balance of Vitamin D3
       5. Down-regulates aromatase which breaks down testosterone among other hormones thus raising testosterone and lowering estrogens
       6. Up-regulates (increases low levels of) VEGF
          1. If Actos or fish oil/omega-3 doesn’t work, VIP will correct the low VEGF
       7. Warning Re; VIP may cause Lipase to increase a bit; measure baseline and monthly X 3 VO2max
       8. Immunoregulatory; this is a Neuro-Immune link
       9. Drives up CD4 + CD25 + FoxP3
       10. Reduced SOB/Cognitive problems
       11. Reduced joint stiffness in ~10 minutes (causes endorphin release)
       12. Improved exercise tolerance
       13. Global improvement in all modalities
       14. Main effect immediately is endorphin mediated…
           1. Typically within 5 minutes of first dose pt’s can take a deeper breath
           2. Joint symptoms @ baseline; tight clenched hands will typically open and relax on VIP
           3. Immediate pain relief is a big deal and much appreciated
       15. Cognitive issues respond more slowly
           1. Draw blood at baseline (Lipase, VEGF, C4a, TGF β-1), give VIP, repeat draw (VEGF, C4a, TGF β-1) in 15 minutes
           2. If there is a sudden increase in TGF β-1, there has probably been recent exposure to WDB with ongoing mycotoxin exposure.
       16. VIP 50-mcg qid corrects paradoxical rise in PASP in exercise in days, not weeks, with durable effects with titration to bid and over time, discontinuation!
       17. **VIP** **Trial Protocol**
           1. At the end of a month of qid VIP, repeat lab parameters
           2. Most people, after 6 months can tolerate a reduced dose of VIP from qid to bid, sometimes to qd
           3. This VIP intranasal protocol has essentially cured a large group of chronic fatigue patients.
           4. FDA has designated VIP for treatment of Pulm Htn (other uses are off-label)
           5. Remember, if using VIP then sustaining exposure to toxin/WDB etc., everything “goes back to square one”.
              1. The response will be truncated and shortened however after recovery from symptoms by a course of VIP.
              2. Patients will tolerate longer periods of exposure as well.
   12. CD4+, CD25+
       1. CD4+, CD25+ are regulatory T-Cells detected on a flow-cytometry assay
          1. CD4+, or CD25+ don’t give useful information
          2. The COMBINATION of CD4+ AND CD25+ provides the useful data
          3. There really are no “normal” ranges
             1. Levels <15 abnormal
             2. 17 for controls
             3. 18 for treated
             4. 25 for VIP
             5. 30’s for Multiple Sclerosis patients on Methotrexate

MTX probably helps connective tissue diseases by driving up the CD4+/CD25+, but that’s just Shoemaker’s speculation…

Plaquenil may work the same way…

* + 1. FoxP3 is a nuclear replication factor that provides greater sensitivity than CD4+ and CD25+
  1. What you need to know
     1. Symptoms must be present
     2. Labs must be done to show…
        1. What is and…
        2. What is not
     3. Differential Diagnosis must be present and documented
     4. Treat only ONE THING AT A TIME and monitor therapy effect
     5. Labs will show you the way
        1. Start looking at innate immunity as a target
        2. Start looking at targets that you can fix
        3. Fix the targets; watch the illness disappear
        4. Wait for relapse
  2. Treatment Message:
     1. *Look* for environmental exposures or *re-exposures*
     2. Establish a decent baseline of results of innate immunity testing
        1. A baseline on controls is just as important as a baseline on ill patients
        2. Follow the normal patients with susceptible haplotypes
           1. Intervene when they fall
           2. Look for VCS, MARCoNS
        3. Fix them quickly so that you can have short interventions and minimal suffering
     3. Look for biofilm formers; they must be eradicated!
     4. Treat the inflammatory physiology
     5. What is left?
     6. What happens when the injured patient is exposed next week?
     7. Repeat illness, requires that the starting point be used to initiate new therapy.
  3. Conclusions;
     1. An organized, data-driven approach to diagnosis leads to effective treatment
     2. Look for the final common pathway
     3. Guessing, assumption and “clinical experience” are of no help compared to data collected with a 30,000 foot view
        1. If you must guess or make an assumption, document that you are doing so!
     4. Hope for cure is here: let’s not forsake our new knowledge
     5. VIP has brought the word “cure” to this syndrome for the first time.
     6. VIP is the golden goose; *don’t kill it!*
  4. For more information:
     1. [www.survivingmold.com](http://www.survivingmold.com/)
     2. [www.chronicneurotoxins.com](http://www.chronicneurotoxins.com)
     3. Surviving Mold December 2010
     4. Mold Warriors 2005, 2007, 2010
     5. Desperation Medicine 2001, 2006, 2009
     6. Lose the Weight You Hate 2002, 2005

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1. **[The Biotoxin Pathway:](http://www.survivingmold.com/docs/biotoxinpathway.pdf)** 
   1. Key Points
      1. There is differential susceptibility based on genetic coding of the individual
      2. This a *host* response, not a *dose* response
   2. Sequence of the pathway
      1. Toxin exposure occurs in an HLA non-susceptible individual
         1. In non-susceptible people, toxins are removed by the liver or broken down by the immune system. Components are excreted harmlessly.
      2. Susceptible individuals with appropriate HLA types have a worse outcome;
         1. Nerve cells are affected directly, impairing function
            1. Abnormal VCS test results
            2. Ciguatoxin affects Na channels in axons
            3. Pfiesteria causes a neurotoxic effect
         2. Adipocyte surface Toll receptors bind the toxin
            1. Leptin increases

Fat cells produce more leptin leading to a vicious cycle and obesity, more leptin production, produces more fat cells…

Leptin receptors of the Hypothalamus are activated

* + - * 1. Cytokine levels increase directly from toxins

Hypothalamic leptin receptors can be damaged by cytokines

* + - * 1. Hypothalamic Melanocyte Stimulating Hormone (MSH) Decreases causing myriad effects as below
    1. Cytokine increase from Toxins and Adipocytes affect;
       1. Capillaries
          1. Hypoxia inducible factor (HIF)

Has many gene activations under its control

Has a role in a variety of illnesses

Influences VEGF, TGF β-1, erythropoietin, platelet derived growth factor

* + - 1. Increased WBC activity
         1. The toxins affect sodium channels on dendritic cells directly.

HLA DR is a “signal molecule” that helps phagocytes migrate to antigen quickly after prior exposure

Cytokines help phagocytes migrate and cause the phagocytes to release more cytokines for an amplification effect

Cytokines bind to leptin receptors in the ventral medial nucleus of the hypothalamus blocking it’s activation by leptin

Leptin is an adipocyte cytokine that works in the hypothalamus to produce endorphins and MSH

This causes fatigue due to the low MSH effects and obesity due to increased leptin amplification and pain due to reduced endorphins

And all the while, people look OK, not ill.

* + - 1. Leptin has it’s own broad range of effects in the hypothalamus causing production of
         1. VIP
         2. MSH (sometimes this reverses with DDAVP)
         3. AVP
      2. Leptin receptor issues cause refractory weight problems
         1. Check Leptin and insulin (or C-peptide) levels in obese patients—they’re probably high, leptin may be >25, but even low leptin levels with these folks don’t help due to low MSH
         2. Actos/low amylose diet and exercise helps
      3. WBC’s without dendrites are immature and circulating, once exposed to antigen however they
         1. Develop dendrites and stay in the lymph nodes etc.
      4. Decreased capillary perfusion
         1. Tissue Hypoxia should increase VEGF, but CIRS🡪
         2. Reduced VEGF

Deficient if <31

Fatigue, muscle cramps, SOB

Can be relieved with erythropoietin

* + 1. Immune System Effects of Cytokines
       1. Inappropriate immunity/autoimmunity
          1. Antibodies (Ab’s) to myelin basic protein (often from mycotoxins)
          2. Gliadin Ab’s affect digestion
          3. Cardiolipins; affect coagulation

Can cause arterial thrombosis’

Example of a patient who infracted jejunum and ileum after documented chlamydial pneumonia

He had been exposed to mold in his greenhouse, cytokine response to his PNA turned on the cardiolipins which maxed out in the several hundred range

* + 1. Complement activation; the “alternative immune system” noted by increased levels of C3a, C4a
       1. Cytokine Related;
       2. Symptoms
          1. Headache
          2. Myalgias
          3. Temperature regulation issues (sweats/fever/chills)
          4. Brain fog
       3. Lab abnormalities;
          1. TNF
          2. MMP9-delivers inflammatory mediators to; blood, brain, muscle, lungs, joints
          3. Interleukin 1b
          4. PAI1 combines with MMP9 to increase clot formation and arterial blockage

PAI1 contributes to ASCVD, is higher in diabetics, explaining their increased risk of ASCVD complications

T-Regulatory cells can convert to pathogenic T-cells

* + 1. Effects of low MSH;
       1. Sleep disturbance (reduced melatonin)
       2. Chronic Pain (suppressed endorphin production)
          1. Enthesopathy at muscle-tendon junction due to hypoperfusion
       3. GI problems (malabsorption-fat, B12; diarrhea, leaky gut-may resolve with restoration of MSH/may be permanent, similar to but is not celiac disease, must avoid gluten, whey, amylose)
       4. Prolonged illness (WBC’s lose regulation of cytokine response—recovery from illnesses is slowed)
       5. Resistant Staph (in mucosa 2’ to biofilm and production of substances that exacerbate high cytokine/low MSH levels)
          1. Do the [API staph](https://www.dxos.com/mold-illness-testing/) and prepare to start BEG spray
       6. ACTH/Cortisol changes (Pituitary produces high ACTH/Cortisol initially, then adrenal exhaustion produces low levels but pt’s must avoid steroids which further lower ACTH); 65% may have
          1. ACTH >45, Cortisol<6 or Cortisol <12 with ACTH <10
          2. Cortisol>18, ACTH<5 or Cortisol >18 with ACTH <20
          3. This reflects dysregulation of the HPA axis/poor feedback control “adrenal fatigue”
          4. VIP will help re-regulate this

Be careful with steroids!!

* + - 1. Reduced sex hormones
         1. MSH has a huge effect on FSH/LH
         2. Menstrual irregularities probably have a hypothalamic basis, not an ovarian basis, may respond to VIP as well
      2. Reduced ADH from pituitary leading to polydypsia/polyuria/electric shocks
         1. Replenish their intravascular volume before dumping Florinef on them.
    1. Phases of Biotoxin Pathway
       1. Stage I; Biotoxin effects
       2. Stage II; Cytokine effects
       3. Stage III; Reduced VEGF effects
       4. Stage IV; Immune effects
       5. Stage V; Low MSH effects
       6. Stage VI; Drug-resistant Staph/biofilm effects
       7. Stage VII; Pituitary effects
  1. Genomics
     1. There are many gender differences in gene activation with inflammation.
     2. This is the cutting edge; where the new advances will occur; it may replace haplotyping as a better, more specific alternative.

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1. **The Academic basis of treatment of CIRS from WDB’s; Objective Physiologic Measures Characterize Treatable Disease**
   1. Once recognized, you’ll see it everywhere
   2. The approach to the problem:
      1. Evidenced-based medicine
      2. Rigorous, transparent, thorough
      3. Differential diagnosis is ever ongoing
      4. No room for assumptions
      5. No room for guesses
      6. The GAO says to document therapy to confirm causation
   3. Define “Damp”
      1. Water intrusion > 48 hours; 2 days!
         1. Water heater/plumbing leak etc.
         2. Pfiesteria ecology in the wild parallels indoor mold environment
         3. What you find indoors is not the same as what you find outside
            1. Even within the same species; Aspergillus is different indoors and outdoors
            2. Less competition for the energy sources indoors; fungi grow faster
            3. 1 square inch is 250,000 organisms, all making spores
            4. Spores break into smaller fragments within hours, these are also antigenic/inflammagenic even if they can’t form new fungi
            5. They create volatile organic compounds (VOC’s) and mycotoxins
            6. Adhesive tape applied to the mold colony and send the tape to a lab for ID
            7. ERMI testing is the best way to get adequate data, results in a week for $300.00
      2. Presence of microbes
         1. Bacteria
         2. Mycobacteria
         3. Molds
         4. Actinomycetes
         5. Byproducts of above
      3. Presence of speciated organisms
      4. Presence of visible mold
      5. Musty smells
         1. Geosmin is the most common compound to create musty smells from fungi, especially from Actinomycetes which is actually bacterial
   4. Don’t call it mold
      1. Toxigenic sources of inflammation found in WDB’s are fungi, Actinomycetes, bacteria, mycobateria
      2. Inflammagens are VOC, beta glucans, hemolysins, mannans, proteinases and mannose-containing glycoproteins (more)
      3. Smaller particles are far more important than larger-sized spores.
      4. Get the picture in your mind that adding water to an environment creates a new ecosystem that is colonized.
         1. “If you wet it, they will grow!”
      5. Air sampling is worthless; you must use ERMI
      6. Comparison of indoor vs. outdoor fungi is also worthless and outdated!
   5. Environmental Relative Mold Index (ERMI);
      1. 2006 EPA and 1,000 homes
      2. Settled dust in two locations
      3. 134 species with Quantitative Polymerase Chain Reaction (QPCR)
      4. Distilled to 26 species from group I, which were water-damaged buildings, then 10 species from group II, which were non-water damaged buildings.
      5. Add sum of logs; subtract II from I
         1. If >2.0 it’s a toxic bldg.; illness will occur, not a question of if but when
      6. Index is a number that represents building health ONLY
   6. Problems with ERMI;
      1. Dividing water saturation into low, middle and high makes sense
      2. Organisms in these micro-ecosystems are different
      3. 5 Aspergilli (middle-wet conditions)
         1. fumigatus
         2. niger
         3. ochraceus
         4. penicilloides
         5. versicolor
      4. Chaetomium and Stachybotrys (Grows in wet-wet)
      5. Trichoderma and Wallemia (dry-wet conditions)
      6. Air sampling won’t allow speciation to this degree
      7. There are about 300 Aspergilli and 200 Penicillii; most are non-toxic
      8. Another problem is that periodically fungal nomenclature changes courtesy of the microbiologists
      9. The ERMI process was arbitrary
      10. The number doesn’t include other organisms that matter or synergism
      11. Somehow, there are lab differences;
          1. <http://www.mycometrics.com> is a good lab
          2. It’s probably best to stick with one lab
      12. Swiffer testing allows sampling to proceed without vacuuming
   7. ERMI is a building index; what about a human health index?
      1. Causality at baseline works (GAO)
      2. Case-control studies say a problem exists
         1. This has been reported in over 50,000 patients in 14 separate countries.
      3. The gold standard is prospective exposure, amply controlled
      4. That’s how we determine risk.

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1. **Sequential Activation of Innate Immune Elements** **(****SAIIE)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Baseline** | **Day 1** | **Day 2** | **Day 3** |
| **VCS** | - | Deceasing | Decreasing | Decreasing |
| **C4a** | - | Increasing | Increasing | Increasing |
| **VEGF** | - | Increasing | Decreasing (2’ to TGF β-1) | Decreasing |
| **Leptin** | - | Stable | Increasing | Increasing |
| **MMP9** | - | Stable | Spikes | Increasing |
| **vWF Factor VIII** | - | Decreasing | Increasing | Normalizes |
| **vWF Ristocetin** | - | Normal | Decreasing | Decreasing/may bleed on day 3 |
| **CD4+CD25+** | - | Decreasing | Decreasing | Decreasing |
| Compare to baseline; |  | C4a, VEGF | Leptin, MMP9 | MMP9, CD’s, VEGF, & symptoms |

* 1. *There must be NO associated re-exposure activities*
  2. This is a prospective exposure trial
     1. Requires informed consent
     2. People who have been sickened and treated, then
     3. Without medications on-board, are willing to re-expose themselves to a WDB
  3. Measures;
     1. A series of labs and health symptoms over *3 consecutive days* of exposure to a given building
     2. Changes in VCS if available will fall in 1-2 days
        1. Neuronal injury happens *after* the cytokine response
        2. C4a is another good measurement to take post-exposure
        3. Persistently elevated C4a can be due to Lyme or Lupus; VEGF can remain altered.
     3. VEGF will rise on post-exposure day (PED) 1, then…
        1. TGF β-1 lowers VEGF
        2. If TGF β-1 remains high or symptoms persist despite normal VCS, Clean ERMI, No MRCoNS, treat with nasal VIP.
     4. VEGF will spike on day one then start to fall due to the effect of TGF β-1
     5. On day 2, Leptin rises
     6. MMP9 spikes between day 2 and 3; it’s made in endothelial cells, monocytes and macrophages.
        1. This will have a gene-transcription time delay, then
        2. A conversion of the pro-metabolite MMP14 which is cleaved to produce MMP9
        3. If MMP9 remains elevated, consider infection, autoimmune or neoplastic process.
        4. VIP may help lower refractory elevation of MMP9
     7. VonWillebrand’s factors
        1. Factor 8 is an acute-phase reactant; it drops after PED 1, on day 2,3 it reverts back to normal as it recovers
        2. Ristocetin associated cofactor and VonWillebrand’s antigen are slower to react
           1. On day 1 are normal
           2. Decline by day 3
           3. Bleeding, if it will occur, will happen on PED 3.
        3. Check VonWillebrand’s profile if hemoptysis and/or epistaxis
        4. LabCorp does not have a good vWF profile, Quest’s is excellent, but costs $575
     8. People who have already been primed will bleed quicker.
     9. “Sicker quicker”
        1. The Human Health Index is based on the previously discussed physiology.
        2. The SEQUENTIAL activation of innate immune elements (SAIIE)
  4. VCS Interpretation
     1. The patient should be able to see beyond 6 in row C
     2. The patient should be able to see beyond 5 in row D
     3. The patient must pass all four of the above measurements (each eye in C & D)
     4. First, check to ensure that both eyes are > 20/50 in acuity at 14” (near vision)
     5. If patient has a far-vision contact in one eye and a near-vision contact in the other, then only the near-vision eye can be used.
     6. This exam is pass/fail; if any one eye can’t see every image necessary, the test is a “fail”; there are no “almost’s”, one miss is a failed test.
     7. It’s an ELEGANT tool to show improvement within a week of Cholestyramine
        1. Scores will improve in row E, then row D…
  5. What is normal SAIIE?
     1. Control buildings; N=50
        1. SAIIE=6.3
     2. Remediated buildings: N=12-
        1. Some high (>15)
        2. Some low (<9)
     3. WDB without remediation; N=160
        1. Mean 17.9
  6. SAIIE meets ERMI
     1. If the MSH is <30, any ERMI >2 is dangerous
     2. If any C4a by RIA is >20,000, the “safe” ERMI falls to -1
     3. SAIIE assumes no other re-exposure activity; this must be verified with VCS
     4. Sequential activation of inflammatory elements is weighted by time of exposure.
  7. Definitions;
     1. HLA DR is done by PCR
     2. C4a
     3. TGF β-1
        1. Has an undeserved reputation of being an *anti*-inflammatory compound
        2. Untrue if it is turning on TH17 cells at the same time with conversion of T-Reg cells *in tissue* into pathogenic T-cells
     4. MSH
     5. VIP
     6. MMP9
     7. VEGF
     8. VCS
     9. VWF (or vWF) (VonWillebrand’s Factor)
     10. Autoimmunity
         1. AntiCardioLipin Ab’s ACLA & AntiGliadin Ab’s AGA
     11. T-Reg Cells (activated in the *circulation* by TGF β-1)
         1. CD4+
         2. CD25+
         3. FoxP3
  8. Cases vs. Controls
     1. How many of these abnormalities can a given person have?
     2. Look at each of these as independent variables, start multiplying p values, the numbers are staggeringly against the possibility of these results being due to chance
     3. Then add cohorts of several patients in the same family/environment/home with
     4. The same haplotypes

|  |  |  |  |
| --- | --- | --- | --- |
| P value <0.001 | Cases | Controls | Significant? |
| Total Symptoms | 22.1 | 3.1 | Y |
| VIP | 7.1 | 35.5 | Y |
| MSH | 9.8 | 34.9 | Y |
| MMP9 | 510 | 260 | Y |
| ACLA-IgM | 34% | 3% | Y |
| AGA-IgG | 41% | 4% | Y |
| C4a | 10,640 | 2,324 | Y |
| TGF β-1 | 8,296 | 2,076 | Y |

* 1. Results; Labs are not different
     1. P>0.05 (usually >0.4)
        1. ESR, CBC, CMP
        2. ESR, CRP
        3. TSH, Cortisol, Testosterone
        4. Lipids
        5. C3, C4
        6. IgE, Immunoglobulin panel
  2. So what is the SAIIE Protocol?
     1. Part of the repetitive exposure protocol
     2. After showing no other building makes the patient ill, patient comes off of medications, re-enters the suspected building for 8 hours on day 1
     3. Measure labs in AM, then re-expose on day 2
     4. Measure labs in AM, then re-expose on day 3
     5. Measure labs in AM, and then resume medications.
  3. Score the SAIIE;
     1. Compare the C4a on day 1 to baseline
     2. Compare Leptin on day 2 to baseline
     3. Compare MMP9 as average of day 2 and 3 to baseline
     4. Compare VEGF to baseline; rise on day 1, fall by day 3
     5. Compare symptoms day 3 to baseline.
     6. Add the values
  4. SAIIE Scores are NOT subtle;
     1. 5 for 100%; 4 for 80%, 3 for 70%, 2 for 60%, and 1 for 50%
     2. Controls mean is 6.3
     3. Cases mean is 17.9
     4. TGF β-1 is a new player, rapidly changing
     5. CD4+CD25+ show promise; it drops rapidly.
  5. What is SAIIE really showing?
     1. We’re looking at the progression of innate immune responses
     2. Hyperacute (C4a and TGF β-1
     3. Gene activation following receptor resistance (leptin)
     4. Bottom line; this is absolute proof of causation.
     5. A/B/B’/A/B research design.
        1. A Person at baseline
        2. B Intervention fixes them
        3. B’ Stop medicine
        4. A Re-expose
        5. B Intervention fixes them again
  6. What then, is the illness?
     1. Pattern recognition; antigen presentation gone awry
     2. Inflammatory responses aren’t controlled
        1. The neuropeptides are gone
     3. Innate immune abnormalities become chronic as a host-response syndrome
     4. ICD-9 and V-codes are available for these;
        1. Therefore a chronic systemic inflammatory response syndrome (ICD-9 995.93) or hazardous effect of exposure to mold (v87.31) = CIRS-WDB.

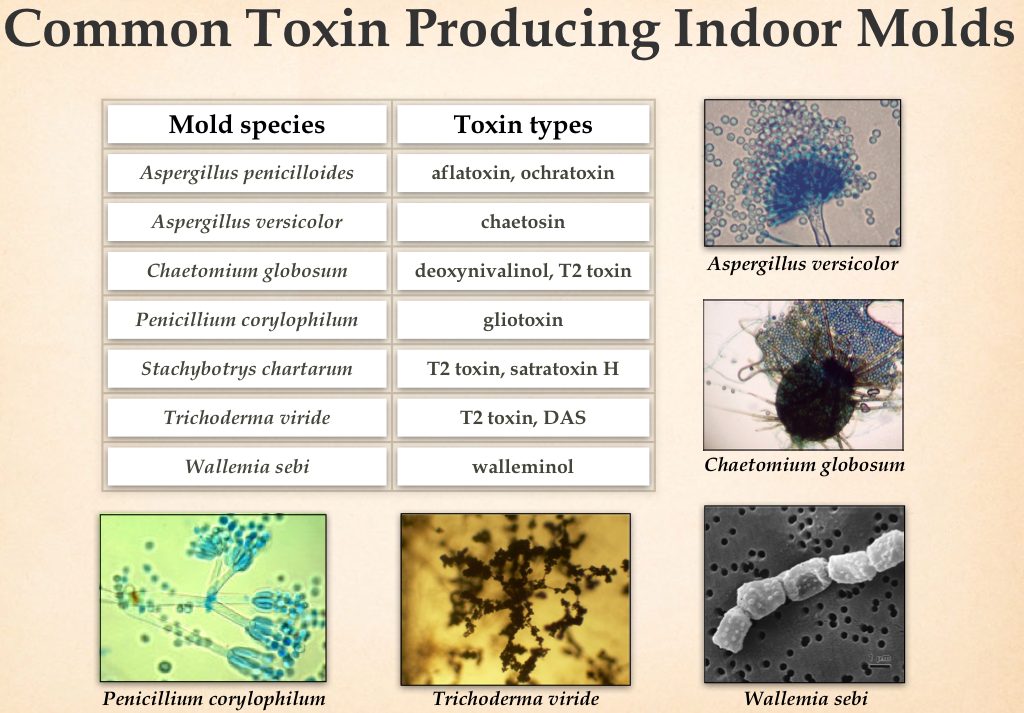
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1. **CIRS**
   1. Once you recognize it one time, your life as a physician will be changed forever
   2. Lack of regulation of inflammation
   3. Enhanced/increased innate inflammatory parameters
      1. Numerous;
         1. C4a, possibly C3a if intravascular membranes
         2. TGF β-1
         3. MMP9
         4. Complement activation
         5. Coagulation activation
         6. Cytokine activation
         7. MSH deficiency
         8. VIP deficiency
         9. Regulatory peptide failure
      2. Hormone dysregulation
      3. Hypoxia from capillary hypoperfusion
      4. Cellular immunity (Th-17, Pathogenic T-reg cells)
      5. Colonizing commensal MARCoNS
      6. vWF factor 66% is abnormal; are these acute reactants? NO
      7. Autoimmunity like crazy!
         1. AGA, ACLA, ANA, ANCA, actin
      8. Cellular immunity, TGF β-1
      9. Activated complement split products
         1. C3a, C4a
      10. CIRS is a systemic, interacting syndrome
      11. There is no way that just one lab value can be the source of
          1. Fatigue
          2. Cognitive dysfunction
          3. Arthritis
          4. Respiratory problems
      12. All of the putative diagnosis’ have the *same final common pathway* in just about every disease we have
          1. ASCVD
          2. DM
          3. MS
          4. Parkinson’s disease
      13. The same combination of multi-symptom illness and lab abnormalities repeat in each patient
      14. Differential diagnosis is key!
          1. All of these various diseases have the same common final pathway
          2. Is there something contributing to a known illness that is NOT from WDB?
             1. YES!
             2. If you want to help these patients, correct the abnormalities that you look for and find.
   4. Let’s not forget genetics
      1. Learn HLA DR by PCR (SSOP)
      2. Look for 4-3-53 (0401, the worst of 12)
      3. Look for 11-3-52B (this one is easy)
         1. Long arms, long fingers, athletic
         2. Fibrillin cross-linking in collagen shortens the range of motion.
         3. Fibrillin cross-linking in collagen binds TGF β-1
         4. With free/unbound TGF β-1, they get “sicker quicker” upon exposure
      4. The “dreaded”
         1. Worst TGF β-1
         2. Most abnormalities

|  |  |  |  |
| --- | --- | --- | --- |
| **HLA Disequilibrium Relative Risk >2.0 Mold Illness Cases** | | | |
| **HLA DR** | **Control** | **Cases** | |
|  | **Adult** | **Child** |
| **4-3-53** | - | 3.6 | 4.4 |
| **7-2/3-53** | - | 2.3 | 2.1 |
| **11-3-52B** | - | 2.9 | 5.3 |
| **12-3-52B** | - | 2.9 | 2.6 |
| **13-6-52ABC** | - | 2.1 | - |
| **17-2-52A** | - | 2.6 | - |
| **48 Other Linkages** | - | - | - |
| **N=** | **457** | **4,960** | **470** |

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1. **Biotoxins**
   * 1. Their very low molecular weight/small size is an indicator of their potential to be ionophores (able to move between cells), they’re made by many different types of organisms.



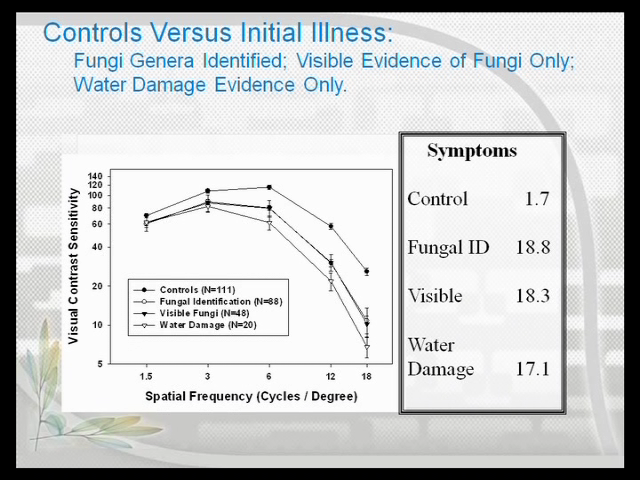
* + 1. Types of Biotoxins

|  |  |  |  |
| --- | --- | --- | --- |
| **Types of Biotoxins** | | | |
| **Agent** | **LD50** | **Molecular Wt.** | **Source** |
| Botulinum | 0.001 | 150,000 | Bacterium |
| Shiga Toxin | 0.002 | 55,000 | Bacterium |
| Diphtheria Toxin | 0.10 | 62,000 | Bacterium |
| Maitotoxin | 0.10 | 3,400 | Marine Dinoflagellate |
| Ciguatoxin | 0.40 | 1,000 | Fish/marine Dinoflagellate |
| Batrachotoxin | 2.0 | 539 | Arrow-Poison Frog |
| Ricin | 3.0 | 64,000 | Castor Bean |
| Conotoxin | 5.0 | 1,500 | Cone Snail |
| Tetrodotoxin | 8.0 | 319 | Puffer fish |
| αTityustoxin | 9.0 | 8.000 | Scorpion |
| Microcystin | 50.0 | 994 | Blue-Green Algae |
| 1. Sarin | 100.0 | 140 | Chemical Agent |
| 1. Aconntine | 100.0 | 647 | Plant (Monkshood) |
| T-2 Toxin | 1,210.0 | 466 | Fungal Mycotoxin |

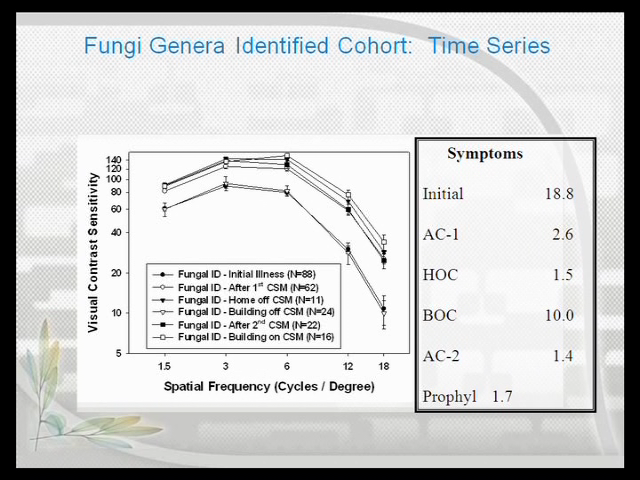
* + 1. Table above showing size and LD50 of selected toxins
    2. Inflammagens bind to receptors
       1. Toll; mannose
       2. Ficolins; C-linked lectins
       3. These produce predictable inflammatory results
    3. Direct neurotoxicity
    4. Involves defective antigen presentation
  1. Antigen presentation
     1. Antigen detection will continue until antibody formation occurs
     2. Internalization of receptor/antigen complex
        1. Phagocytosis is an innate immune function
     3. Acidification of phagoendosome which is then presented to the
     4. Endoplasmic reticulum producing the phagoendolysosome, then the
     5. ER adds HLA DR in the ER of dendritic cells and present it to
     6. Naïve T-cells and to B-cells found in lymph nodes, not in circulations
  2. Ways to disrupt the antigen presentation sequence;
     1. Trichothecenes disrupt membrane associated liganding CD 80/86
     2. Polycyclic ethers stop acidification
     3. Bordetella toxins have intracellular targets (pertussis-defective Ag presentation)
     4. HLA as ligand is blocked by high IL-10
        1. IL-10 is an immune paralytic!
     5. CLTA blocks T-Cell adhesion
     6. T to B cell??
  3. So what?
     1. If we don’t have antigen (Ag) presentation, will there be antibody (Ab) formation? No
     2. If no Ab is formed, will Ag be cleared? No
     3. If no Ag is cleared, will there be a persistent Ag activation of innate immune responses? Yes
     4. And then, if there is persistent Ag activation, will dysregulated innate immune response ever cease? No
        1. So if you remove the source of exposure, will you heal? No
        2. If you deal with allergy, irritation or many other noxious agents remove the exposure and the reaction will cease.
        3. Not so with CIRS!
  4. Ag detection sets off the *amplification cascade*
     1. Use any image you want
        1. Barking dogs, sentry, firecrackers
     2. Complement, cytokines are pre-formed
     3. Differential gene activation follows
     4. Interaction of endothelial cells, macrophages, monocytes, hypoxia induced factor (HIF) is next, then hopefully it is
     5. Controlled by MSH & VIP.
  5. Without Ab, neuropeptides won’t control inflammatory responses
     1. Uncontrolled amplification cascade🡪CIRS
     2. MSH is the first to fall
     3. Cytokines bind to long isoform of the leptin receptor; no POMC is made.
        1. Another action of circulating pro-inflammatory cytokines is the stimulation of leptin release from adipocytes.
        2. Leptin has two important functions in the biotoxin pathway,
           1. Triggering macrophage synthesis of additional pro-inflammatory cytokines in a positive feedback loop and
           2. The *initiation of negative feedback control on cytokine production through the proopiomelanocortin (POMC) pathway in* the ventromedial nucleus of the hypothalamus forming MSH & endorphins.
        3. Leptin-POMC lowers cytokine levels.
        4. Leptin links neuroendocrine and immune systems by binding to the long isoform of the leptin receptor, which resembles a gp-130 cytokine receptor, thereby stimulating POMC expression and depolarization of POMC-containing neurons <http://www.survivingmold.com/docs/Resources/Shoemaker%20Papers/NTT5863.pdf>
     4. *Without POMC, then no MSH and no beta endorphin* 
        1. But there is plenty of fatigue, weight gain and pain
     5. Next is VIP
        1. cAMP, Regulation Pulmonary Artery Systolic Pressure

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1. **Diagnosis is not just exclusion**
   * 1. Chronic multisystem, multisymptom illness refractory to all interventions.
     2. Dense innate immune abnormalities are invariably present
     3. Genetic basis; (HLA DR by PCR)
     4. Onset is the end of the diagnosis
        1. Numerous other aspects/complications are comorbid
     5. Ongoing effect of environmental exposures
        1. This is critical; don’t forget this!!
           1. Sicker Quicker
           2. Back to “square one” if re-exposed, starts with removing exposure.
   1. Start with **V****CS** if you’re going too start
      1. Simple
      2. Old neurotoxicology test—but still works well
      3. On-line versions vary
      4. Diagnosis at baseline and essential for follow-up
         1. Especially with hyperacute patients
      5. Correlates with measures of retinal capillary perfusion
      6. Used since 1970’s by DOD/USAF and in studies of non-biological toxicants
      7. Reproducible, reliable, portable, non-invasive, cheap
      8. The best marker beyond day 4 of biotoxin-associated cytokine disease
      9. Neurologic function of optic nerve/vision
      10. Eliminates near, far, color, static, motion, peripheral vision
      11. Visual non-invasive measure of contrast
      12. Requires corrected visual acuity >20/50
      13. Control light @ >70 foot-lamberts of light intensity with light-meter
          1. Two 15 inch fluorescent lamps
          2. With “daytime color” lamps provides adequate light for the test.
      14. Used in prior studies: screening/monitoring.
   2. Controls vs. Initial illness;
      1. Curves represent; Control, Fungus identified, Visible evidence of fungi only, visible evidence water damage only



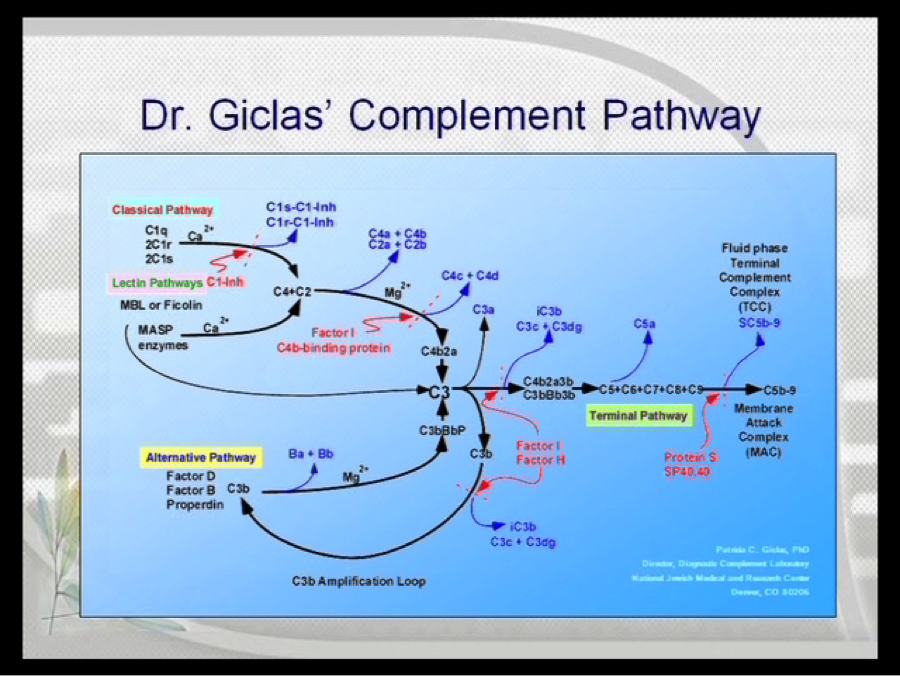
* + 1. Results are not subtle
    2. Only air sampling was done to identify fungi,
       1. Genus available only, not species
       2. Not done with more appropriate ERMI testing (precedes ERMI availability)
    3. P-value <0.001; highly significant/not due to chance
    4. Patients testing positive were highly symptomatic
    5. Visual abstract mathematical functions drops out quickly too; ask the patient to mentally divide 91 by 11 (91/11=8.27 “eight with a remainder” is good enough).
    6. Bottom curve/worse results of all were water damage and musty smell
       1. *No mold was identified at all!*
  1. Fungi genera identified cohort; Time series



* + 1. Symptom/Curves represent (top to bottom)
       1. Initial; Sick patient untreated
       2. AC-1; Treated
       3. HOC; Improved post-therapy
       4. BOC; Stop medication/Cholestyramine (low symptoms)
       5. AC-2; Re-exposed to the WDB without Cholestyramine
       6. Prophylactic; Returned to the WDB while taking Cholestyramine
    2. Similar curves are generated regardless of type of building
       1. Home
       2. Work
       3. School
    3. There are usually mixtures of organisms and toxins involved in these cases
       1. It’s generally impossible to say which toxin or which organism caused the damage
       2. Damage was likely caused by numerous organisms and toxins
       3. Genomic studies when available will help to solve this dilemma
    4. Pax-gene testing

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1. **Case Studies:**
   1. Case study; 49 yo WF, ill X 4 years, school teacher
      1. Delayed recovery from normal activity
      2. Unremitting fatigue, cognitive issues, arthritis
      3. Differential Dx; nothing confirmed
      4. Multisystem/multisymptom illness
      5. Denied disability; deemed “psychiatric” by insurance company
      6. Fibromyalgia per rheumatologist; trial of Lyrica
      7. XMRV said the WPI user per CFS patient
      8. Lyme said the Lyme-Literate local DM
      9. Innate immunity is at your service, but you must ASK!
         1. Does she have excessive inflammatory responses? (Yes)
         2. Does she lack regulation of immune response (IR) as shown by neuropeptide deficiency? (Yes)
            1. MSH (low/undetectable; <8)
            2. VIP (low/undetectable; <10)
      10. What does the VCS show? (+) (Not XMRV which will not cause VCS (+))
      11. Are there problems with;
          1. TGF β-1 (elevated; 15,097, normal <2,380)
          2. MMP9 (elevated; 673, should be half of this)
          3. VEGF (depressed; <31, low VEGF expected with high TGF β-1)
          4. Cellular immunity (yes; “c”, below)
          5. ACLA (+ cardiolipins) IgM (revealing T-cell dysfunction)
          6. Activated complement (C4a) (elevated; 10,344, normal <2,830)
          7. Coagulation (thrombophillic)
          8. ADH <0.9 with Osmolality 316 (dehydrated)
          9. MARCoNS by API-staph (six classes of resistance! She had been on different types of antibiotics for 6 months)
          10. HLA 11-3-52B and 4-3-53 (each of the dreaded)
          11. (Yes indeed to a-k, 9, 10))
      12. Is this CRS
          1. ABSOLUTELY! (ICD-9; 995.93)
   2. Case Study; Simple mold case
      1. WDB have lots of toxins and inflammagens
         1. Use ERMI!
      2. No specific causation (which organism or toxin made her ill?)
         1. Too many complex issues to be able to tell due to so many potential causes that probably interact with each other to cause patient problems.
         2. Bacteria, Actinomycetes, fungi
         3. Beta glucans, mannans, hemolysins, VOC’s, mannosylated lectins/dectins
      3. WHO (7/09); GAO (9/08); POA (7/10)
      4. Is your differential complete? Did you look for hypoperfusion
         1. MR Spectroscopy to delineate suppressed Glutamate/Glutamine ratio (takes an hour and twenty minutes in the scanner)
         2. MRS to check for elevated lactate alone (with therapy it takes 3 weeks for scans to normalize)
         3. Can you R/O capillary hypoperfusion in CNS by history?
            1. Yes, cognitive dysfunction, executive functions (91/11=8+…)
            2. Generally these are the patients that providers consider as “whacko’s”
         4. How about glial cell production of;
            1. C4a
            2. Reduced VIP
            3. Reduced MSH
   3. What are *environmental sources* of innate immune abnormalities/CIRS?
      1. WDB’s/mycotoxins most commonly
      2. Post-Lyme syndrome (be careful of this)
      3. Ciguatera (under-diagnosed)
      4. Cyanobacteria (usually, but not always due to tropical fresh water)
      5. Pfiesteria (fish kills)
      6. *Recluse Spider* bites with central ulceration (rare)
         1. De-roof the lesion
         2. Topical Cholestyramine binds that reservoir of toxins
         3. Add oral Cholestyramine and Actos together as well to complete the therapy
         4. Cholestyramine topically is also useful for poison ivy patients
            1. Mix a packet of Cholestyramine in a jar of Noxema
      7. Can we define CFS or FMR by biomarkers?
   4. *Biotoxin Symptoms*
      1. Fatigue
      2. Weak
      3. Aches
      4. Cramps
      5. Unusual sharp, claw, electrical
      6. Light sensitivity
      7. Red eyes
      8. Blurred vision
      9. Tearing
      10. SOB
      11. Cough
      12. Sinus symptoms
      13. Abdominal pains
      14. Secretory diarrhea
      15. Morning stiffness
      16. Arthritis
      17. Executive and Cognitive dysfunction (hold the neurocognitive testing, take an exposure history, Pfiesteria provided a great platform to demonstrate when testing in hyperacute and recovery periods were done in cohorts.
          1. Decreased recent memory
          2. Difficulty concentrating
          3. Word-finding difficulty
          4. Decreased assimilation of new knowledge
          5. Confusion
          6. Disorientation in familiar places
      18. Memory loss
      19. Impaired concentration
      20. Trouble swallowing
      21. Assimilation problems
      22. Confusion
      23. Disorientation
      24. Impaired mood
      25. Impaired appetite
      26. Sweats/chills; thermoregulation problems
      27. Frequent urination
      28. Excessively thirsty
      29. Electrical shock sensation when touching skin
      30. Paresthesias/numbness, tingling
      31. Altered taste
      32. Tremor
      33. Vertigo/dizziness
   5. Take a careful history
      1. If you “hit”, look at what you can save the patient;
         1. Patient’s course and outcome
         2. Untold millions (? billions) of dollars
      2. The International Academy of Chronic Fatigue Syndrome changed their approach to Pediatric CFS as their case definition was incomplete
         1. They added mold exposure specifically to their exclusion list
   6. How do we know
      1. Prospective exposures give us causation
      2. Genomic studies from prospective exposures
      3. Defined abnormalities in genomics are persistent and may be unique
         1. This could help to separate
            1. Ciguatera from
            2. Lyme from
            3. Pfiesteria from
            4. Mold toxins, etc.
      4. Could this be a “fingerprint”?
   7. After pattern recognition (involved with Ag presentation)
      1. Pro-inflammatory cytokines
         1. Th-1 followed by Th-2
      2. Complement activation
         1. C3a, C4a, anaphylatoxins
      3. Differential gene activation
      4. Interacting exponential cascade
      5. TGF β-1 and a newly discovered player: Th-17 immunity!
      6. T-reg cell dysfunction
   8. TGF β-1
      1. There are 58,000 references on PubMed as of 5/20/10
      2. Not one commercial lab until 4/08 was testing for it until Cambridge Biomedical began testing
      3. ELISA from R and D Systems
      4. Controls <1,350
      5. Cases average 6,000 pre-therapy
      6. After treatment (all factors\* corrected), average drops to 1,800
      7. \* see [1) Biotoxin Pathway](http://www.survivingmold.com/docs/biotoxinpathway.pdf) High levels of TGF β-1 can also be treated with Losartan (Cozaar) or it’s degradation product; exp3179
      8. Treating high levels of TGF β-1 reduces the driving force between pathogenic T-cells and cellular based immunity & use of VIP.
   9. Meet TH-17; Pathogenic T-Cells that are the main drives of Autoimmunity and Collagen-induced arthritis
      1. More than Th-1 and Th-2
      2. In the presence of IN-6 and TGF β-1, naïve T-cells differentiate into Th-17
         1. In the periphery, they can make IL-10 and pro-inflammatory cytokines
      3. High TGF β-1 is associated with abnormalities in T-reg cells
         1. Inducible T-reg’s add to TGF β-1
      4. High TGF β-1 I innate immune illness is prolonged
         1. It’s also complicated by autoimmunity.
   10. What can go wrong?
       1. This is a dynamic process! Consider
          1. Re-exposure
          2. Absence of antibody formation to stop the process
          3. New exposures
          4. Inflammatory responses are not static
          5. Once the host is altered, the next response will also be altered.
   11. Logistic Regression; Methods
       1. Using a “forward selection” model, allowing all variables that were present for both groups (those with and without mold illness)
       2. Systematically removing variables that produced “quasi-complete separation” (which produces perfect predictability but no measure of variability).
       3. By using symptom clusters and VCS the Dx of CIRS can be attained with 98.8% accuracy at the bedside even before lab results are available.
       4. Final resolution of the CIRS involves correction of the lab abnormalities
          1. You must do the labs initially to have a baseline as well as to secure the Dx
          2. The labs will also help determine which etiology of the CIRS the patient has:
          3. Lyme?
          4. Ciguatera?
          5. Mycotoxins?
          6. Pfiesteria?
          7. Etc.
   12. Does Physical exam help?
       1. Nope, may have mild tremor, low grade tachycardia etc.
       2. Patients look good and feel terrible
       3. Don’t be deceived by their appearances
       4. Take the three minutes to get a decent review of symptoms!!
       5. When you see the internist comment; “Diffusely positive review of systems” beware; Biotoxin illness lurks!
   13. MR Spectroscopy
       1. Methods count
          1. Need to use the same head position during the scan and f/u scans.
       2. Look at the same areas consistently
          1. Bilateral frontal and hippocampal; 1 cm voxel
       3. Look for signal to noise problems
   14. Chemical abnormalities on MRS in Biotoxin illness are absent in psychiatric pt’s;
       1. N-Acetyl Aspartate (NAA); evaluates white matter
       2. Creatine;
       3. Choline; provides information on acetyl choline
       4. Myoinosotol; status of glial cell elements
       5. All of the above are typically wnl
       6. Lactate high (capillary hypoperfusion)
       7. Ratio of excitatory Glutamate to inhibitory Glutamine;
          1. Depressed with brain fog
          2. High in ADHD/Manic
       8. Total is 5.2 in cases; 0.9 in controls
       9. Corrects with erythropoietin in <3 weeks if high C4a
   15. Psychiatric symptoms are often related to inflammation/inflammatory biomarkers
       1. Peripheral Vasoactive compounds cross the BBB and are found in CSF
       2. Central metabolic effects occur (glial apoptosis)
       3. Central metabolic changes; Lactate, Glutamate/Glutamine
       4. Reversed by correction of inflammatory sources and processes
       5. Not corrected by psychiatric medications!
   16. MRS & ERMI scores
       1. Can be correlated in patients with MSH <35
       2. Weighted cognitive symptoms don’t correlate with *range* of ERMI values
          1. It’s almost “all or none”
       3. Total number of lactate and G/G abnormalities
          1. MATCH ERMI!!
          2. MATCH C4a
       4. If ERMI >14, MR Spectroscopy abnormalities >7!
       5. We need more patient data
   17. Biofilm formers; MARCoNS
       1. Not your mother’s Coagulase Negative Staphs
       2. 80% Methicillin resistance
       3. Not seen in one or none resistances
       4. Planktonic organisms become differentiated; multicellular?
       5. Hemolysins
       6. MSH Cleavage factors; low MSH
       7. MARCoNS <https://www.dxos.com/mold-illness-testing/>
       8. We have 6,500 cultures
       9. Biofilm formation is expected
       10. Multiple antibiotic resistance=signifies commensals are present.
       11. You won’t see improvement until MRCoNS is eradicated
       12. Reservoir in dogs noses and wet buildings
   18. MARCoNS Rx is straightforward for now;
       1. Rifampin penetrates biofilm; #2 of the 300 mg tabs q AM
       2. EDTA dissolves biofilm
       3. Muciprocin/Gentamycin synergistic effect
       4. Use above for 1 month
       5. IMPERATIVE; MUST DO THE API-STAPH <https://www.dxos.com/mold-illness-testing/>
          1. When doctors skip the culture…
       6. Very slow growing cultures
          1. What you don’t know will hurt your patient!
   19. Complement Pathway Gicla



* + 1. Ficolin activates MSP2 as part of the mannose-binding lectin associated serine protease 2 mechanism will split
    2. C4 into C4a & C4b then
    3. C2 splits into C2a and C2b
    4. The combination of C2a & C4b with Magnesium fits onto a bacterial membrane, it will then
    5. Split C3 to form C3a (which is an indication of bacteremia/intravascular bacterial membranes).
    6. As a matter of practicality, the turn-around time for C3a & C4a lab results is 3-4 weeks.
       1. LabCorp is considering doing the tests in-house to give results in <1 week
    7. Dr. Shoemaker initially measures C3a & C4a at baseline and at the end of each of the 1-month steps to prove that the diagnosis is mycotoxin related, that the illness is not due to bacteremia or Lyme disease.
  1. Complement Definitions;
     1. C4a; activation of product of C4 by MASP2
        1. No membrane attachment needed
        2. C4a has a very short half-life in blood
        3. The reason for the persistence of C4a in circulation is the absence of clearance of the antigens that turned on the MASP2.
        4. The presence of Ag’s turns on MASP2.
        5. There is an absence of Ab’s to remove the Ag’s thus turning off the MASP2 and the inflammatory cascade.
        6. CIRS happens when there is a lack of resolution/regulation by neutralizing Ab’s to turn the cascade off by removing the Ag’s which would then disable MASP2
        7. MASP2 will thus no longer “auto-activate”, giving the rise to C4a
        8. MASP2 is the key to “sicker quicker”
        9. Ab’s would turn this off if they were present.
     2. C3a; activation product of C3 after C4bC2a combination links to C3 by MASP2 if an intra-vascular bacterial/ricketsial membrane is present for MASP2.
     3. MASP2 auto-activates following pattern recognition of particular glycoproteins by *Mannose Binding Lectin (MBL)*
     4. So far there is no definitive proof by data of VIP inactivating MASP2, but it’s suspected that this is part of the mechanism since patients get so much better so much faster when VIP is used.
        1. There is no big rise in C4a after Ag exposure as there was before use of VIP, so it must involve MASP2
     5. If MASP2 is involved, there is NO self-healing.
  2. C4a;
     1. Putative anaphylatoxin
     2. Measured as C4a by TRIA @ NJC
     3. Split product of complement activation
     4. Activates Mast cells and basophils
     5. Increases
        1. Smooth muscle contraction
        2. Vascular permeability
        3. Release of chemotactic factors
     6. Systemic responses follow activation.
     7. C4a elevations are present in patients with dermatographia due to degranulation of Mast cells
        1. Increases vascular permeability
           1. Fixing C4a elevations can stop pitting edema
           2. ADH deficiency causes dehydration, if there is also edema, look to C4a to be elevated

This patient is not “chronic fatigue”; this is biotoxicity!

* + - 1. C4a activates chemotactic factors
    1. C4a is released by cleavage of C4
       1. Ficolin can trigger this reaction
    2. No receptor for C4a has been identified
    3. C4a is formed by
       1. Activation of the Classical Complement Pathway or
       2. Lectin pathway
       3. Not formed by the Alternate Complement Pathway
    4. Rapid rise in C4a is either from
       1. Ag/Ab complex or from
       2. Lectin binding to carbohydrate groups on bacterial surfaces
    5. High C4a is associated with
       1. Cognitive deficits
       2. Restrictive lung disease (will also have a rise in TGF β-1)
       3. Hypersensitivity pneumonitis
       4. Multi-system, multi-symptom illnesses dominated by chronic fatigue
    6. Re-exposure brings a rise in C4a within
       1. 4 hours in patients exposed to Toxigenic fungi
       2. 12 hours after tick bite in Lyme patients
    7. Elevated levels of C4a persist, even though C4a has a short lifespan
       1. Ongoing immune dysregulation/inflammation is the cause
    8. “Sicker Quicker” for mold people, C4a levels will come down nicely with treatment, but when re-exposed, instead of a mean C4a of 10,000, C4a will jump right to 20,000; relapsing patients jump much higher than initial treatment patients
    9. Treated vs. **Untreated Patient C4a Levels**

|  |  |  |  |
| --- | --- | --- | --- |
| **Untreated Patient C4a Levels** **C4a Summary Page** | | | |
| **Category** | **N=** | **Mean** | **SEM** |
| Lab Control |  | <2,830 ng/ml |  |
| Control | 70 | 2,985 | 132 |
| Acute Lyme ECM- Untreated | 10 | 17,646 | 4,543 |
| Acute Lyme Treated | 5 | 4,196 | 821 |
| Chronic Lyme Untreated | 26 | 8,872 | 750 |
| Chronic Lyme after antibiotics | 11 | 9,349 | 570 |
| Chronic Lyme Treated | 41 | 3,780 | 217 |
| Acute Mold Untreated | 32 | 16,250 | 2,946 |
| Acute Mold Treated | 16 | 4,172 | 521 |
| Acute Mold Relapse | 105 | 22,219 | 1,886 |
| Chronic Mold Untreated | 273 | 12,266 | 699 |
| Chronic Mold Treated | 273 | 4,183 | 157 |
| Chronic Mold Relapse | 70 | 14,138 | 982 |
| DINO Untreated | 11 | 15,461 | 1,121 |
| DINO Treated | 13 | 4,402 | 477 |
| CFS Untreated | 24 | 9,033 | 865 |
| CFS Treated | 11 | 5,837 | 532 |
| EPO Before Treated | 59 | 18,807 | 2,155 |
| EPO After Treated | 40 | 5,741 | 3,836 |
| EPO After Relapse | 31 | 22,103 | 3,399 |
| Relapse by all Illness | 212 | 19,762 | 1,231 |

* 1. C4a in a variety of conditions per table above
     1. People with long-standing Lyme
        1. After antibiotics; no change
        2. After CIRS therapy it falls nicely
     2. Acute mold patients with very high C4a fixed by CIRS down to level of acute Lyme which is close to control patients
     3. Dinoflagellate folks with similar pattern after CIRS therapy
     4. Erythropoietin for the very worst patients doesn’t work quite as well but brings it down quite a bit
     5. Re; C4a and “Sicker Quicker”; the relapsing patients instead of mean around 10K-11K, the mean is 22K
        1. There REALLY is a difference in C4a in the relapsing patients!
        2. To Summarize **Treated vs. Untreated C4a**

|  |  |  |
| --- | --- | --- |
| **Category** | **N=** | **Value** |
| Lab Control |  | 2,830 |
| Control | 300 | 2,985 |
| Untreated All | 4,888 | 12,602 |
| Treated All | 4,392 | 4,193 |
| EPO before | 259 | 18,807 |
| EPO After | 240 | 5,741 |
| Relapse All | 1,603 | 19,762 |

* 1. Treatment;
     1. Remove from exposure
     2. Cholestyramine for 30 days
        1. Actos run-up (if Lyme)
     3. Eradicate biofilm formers/MARCoNS
     4. No gluten if AGA (+)
        1. Do Tissue Trans-Glutaminase IgA, IgG, IgM if Gluten (+)
           1. Expect to find more of the IgG than IgM but measure all 3
     5. Actos/low Amylose diet for MMP9, PAI-1, Leptin
     6. Correct ADH/Osmolality;
        1. Use DDAVP if abnormal
     7. Androgens;
        1. Look at Testosterone/Estrogen ratio’s to determine if up-regulated
        2. Consider DHEA Sulfate to correct from “upstream”
        3. Avoid Aromatase Inhibitors
     8. Fix C3a, C4a, TGF β-1
        1. Losartan 12.5-25 mg bid
        2. Consider VIP therapy
           1. VIP Benefits for abnormal values

Lowers elevated C4a, TGF β-1, VEGF, MMP9, Vitamin D3, reactivity to WDB

Raises low VEGF, Vitamin D3, thymus-derived & induced T-Reg cells

* + - * 1. Potential VIP side effects

May raise lipase levels

Abdominal discomfort 2’ to lowered gastric HCl production

Excessively low BP due to vasodilation

Rash

* + 1. Check VEGF
       1. Consider Erythropoietin
  1. Low Amylose Diet
     1. Foods are converted quickly to sugar in saliva due to amylase
     2. This gives a higher glycemic index
     3. Amylose is the sugar for developing plants, it’s found in;
        1. Seeds
        2. Roots; any root vegetable will have Amylose in it those that seem OK...
           1. Onions
           2. Garlic
     4. Has a different Glucose-Glucose bond than Glycogen
        1. Wheat
        2. Oats
        3. Rice
        4. Barley
        5. Rye
     5. Seeds that have an Amylase inhibitor within them are OK to eat, they include;
        1. Corn
        2. Sorghum
        3. Buckwheat
        4. Quinoa
        5. Amaranth

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1. [**Clinical Course**](http://www.tequestafamilypractice.com/articles/CIRSLabs.xlsm)  **during Treatment of Chronic Inflammatory Response Syndrome** [**(** **Lab Summary)**](#XXISummaryofLabs)
   1. Usually patients with an elevated MMP9 will feel worse when starting Cholestyramine
   2. Lyme patients will often develop an increased MMP9 with therapy, their symptoms and VCS will worsen
      1. If treating Lyme and patient feels worse after start Cholestyramine
         1. Look at VCS row D&E
         2. Repeat MMP9
         3. Stop Cholestyramine
         4. Revisit the issue; Do they have Lyme or other toxin
         5. *If Lyme, don’t resume Cholestyramine*, don’t give antibiotics for Lyme
         6. *Give Actos/low amylose diet*
   3. Some people will get worse initially, but it will only last a couple of days
      1. Lyme patients can go 3-4 days
   4. How does Cholestyramine Work?
      1. Not absorbed, can’t add to host
      2. Binds to anion dipole structures such as quaternary amines, has a net (+) charge, also binds
         1. Cholesterol
         2. Bile salts
      3. It’s basically a biologic glue
      4. Becomes an electron sink
      5. Toxins have an anion ring, sharing electrons
      6. The toxin thus binds to the Cholestyramine
         1. They’re the same size and shape but with opposite net charges
         2. Binds
            1. Pacific and Caribbean Ciguatoxin
            2. Brevitoxin in Dinoflagellates
            3. Ochratoxin in Mycotoxins
            4. Wortmannin
      7. Interrupts enterohepatic recirculation
      8. Stops Ionophores
   5. Then what?
      1. Meet VIP
      2. Deficient in 98% of CFS-type illness
      3. 50 mcg/ml nasal spray qid
      4. An orphan drug used off-label
         1. Designated for Pulmonary Htn
      5. First use in CFS-like illness in 11/08
      6. Response is immediate and dramatic
      7. “VIP puts out the fire and adds a coat of paint”
      8. Vasoactive Intestinal Polypeptide “VIP” is a Regulatory neuropeptide
      9. Hypothalamic suprachiasmatic nuclear agonist neuropeptide
      10. Input from Olfactory bulb and retina
          1. Listen up MCS folks!
          2. One patient uses 8 doses @ bedtime (2 qid didn’t work) great success!
      11. Effector neuropeptide
          1. Increases cAMP; the second messenger intracellularly
          2. Controls Pulmonary Artery Pressure
      12. Don’t abuse it by prescribing when/where it’s not indicated
          1. Don’t use with
             1. Abnormal VCS & ERMI >2
             2. Untreated MARCoNS or
             3. MSH<35
      13. Measuring toxins and cytokines in blood or urine toxins is a huge waste of time/money
          1. They’re not excreted in genetically susceptible people
          2. A new hardware development is a hand-held beta-glucan detector that will show the presence of VOC’s
   6. Usual Disclaimers Re; VIP
      1. VIP is safe, basically impossible to OD
      2. VIP has an excellent record to date
         1. >100 pt’s with Rx filled @ Hopkinton
      3. Easy to use, portable
      4. It works great!
      5. Available by Rx
      6. Just about every CFS’er is deficient in VIP
      7. When word gets out, look out!
      8. Concern; people will leap to it’s use without recognition of what makes it work and when it should NOT be used (L above)
   7. IRB-approved clinical trial
      1. 30 patients; open label
      2. Titration study
      3. Entry criteria include;
         1. ERMI <2, normal VCS
         2. Negative cultures
         3. PASP rise >8 Torr in exercise
         4. MMP9 Normal
         5. C3a Normal
      4. QID X 30d, then BID X 30d, then QD X 30d, off 30d then 6 month F/U
   8. **Clinical R****esults of VIP Therapy**
      1. Before giving VIP, draw baseline; Lipase, VEGF, C4a, TGF β-1.
      2. VIP Lowers C3a/C4a/TGF β-1, Reduces PASP with exercise, Increases VEGF & VO2max, Stabilizes aromatase & Vitamin D
      3. PASP resolved on qid and bid
      4. Normalized capillary hypoperfusion
      5. Symptoms decreased rapidly on qid, increased with downward titration
      6. Normalized C4a & TGF β-1
      7. Normalized VEGF, Androgens (normalized aromatase)
      8. Normalized Vitamin D (unexpected)
      9. At 6 month F/U, no dropouts
      10. Ongoing use of 1-3 doses/d
      11. Consider the illness as treated/controlled
      12. Remember to screen for Lipase with VIP use
      13. Down-regulation of reactivity
          1. Stabilizing MASP2? (yields lower C3a, C4a)
      14. Reduced chemical sensitivity
      15. Enhanced quality of day to day life
      16. Cognitive improvement
      17. Reduction in disability; giving life back to the “living dead”
   9. Discussion
      1. Must use sequential therapy first
      2. Do NOT skip steps
      3. Don’t be creative with database
      4. Don’t fail to correct ERMI, VCS before VIP
      5. Must NOT have ongoing exposure!
      6. VIP is miraculous
      7. VIP has been abused
         1. Not for (+) VCS patients!
         2. Don’t guess about symptoms and PASP; you MUST measure TR/PA pressures!
         3. Don’t even think about starting CIRS therapy with VIP, it’s therapy for THE END!
         4. Document the process
            1. It is off-label use since it’s designed only for Pulm Htn.
   10. Autoimmunity in CFS
       1. Antigliadin IgA and IgG\*
          1. Adults 33%, Children 58%
          2. TTG IgA is used as a F/U confirmation test, not a screening test
       2. Anticardiolipins IgA, IgG and IgM\*
          1. Adults 15%, kids 28%
       3. Anti-Actin (smooth muscle Ab’s)
          1. Adults 10%, kids 18%
          2. Positive in a lot of 11-3-52b’s
          3. Unclear what to do with anti-actin Ab’s in the face of normal LFT’s
       4. ANA 5% in Adults and kids
       5. Control incidence in all <3%
   11. Conclusions
       1. An organized data-driven approach to diagnosis leads to effective therapy!
       2. Guessing, assumption and “clinical experience” are of no help compared to data
       3. Hope for cure is here; let us not forsake our new knowledge
       4. This is the Golden Goose; don’t kill it!
   12. Discussion/audience questions
       1. Chitosan should have the same correct structure to bind anionic toxins
          1. At pH of <9, Chitosan depolymerizes losing an acetyl group
       2. Bentonite clay and activated charcoal have not produced reproducible success
       3. Currently there is nothing that works as well as Cholestyramine and Welchol
       4. Cholestyramine is NOT given to the very severely ill
          1. Use Welchol for these patients
          2. Welchol for MCS patients
             1. Grind it into small pieces and take a looong time to get to therapeutic dose so that it’s tolerable
          3. Cholestyramine is “category C” in pregnancy
             1. You must document that the decision to use the drug has been discussed with the patient, that risk<benefit
             2. The Amish have used Cholestyramine in pregnancy and nursing without any problems.

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1. **Understanding the inflammatory basis of Post-Lyme Syndrome; Objective Physiologic Measurements that Characterize this Treatable Disease**
   1. Goals
      1. Discuss inflammatory elements that contribute to Post-Lyme Syndrome
      2. Discuss therapy of those elements
      3. Provide a framework for evaluating the process of treatment of PLS
      4. Provide indication for abnormality in regulation of T-Reg cells
   2. Agenda
      1. Assumptions are the enemy; don’t guess!
      2. What inflammatory pathways can we define?
      3. Biotoxin Pathway
      4. CIRS
      5. TGF β-1 is your buzz word
      6. C4a & MASP2 are not your friends
      7. CD4+, CD25+, FoxP3+ T-reg’s are key
   3. The ongoing argument
      1. Antibiotics for never (wrong)
      2. Antibiotics forever (wrong)
         1. Is the answer putative co-infections?
         2. Is there MARCoNS?
         3. What does the differential Dx show?
      3. Lyme has been reported from every state in the US including Hawaii!
      4. Both sides need to pay attention to;
         1. Genetics
         2. Markers of innate immune inflammatory responses
      5. Patient outcomes are the only goal
   4. Look at the PLS Assumptions
      1. 90% of Lyme patients have ECM rash (no)
      2. 95% of Lyme patients only need short-term antibiotics (no)
      3. VCS.
      4. Just about every Lyme patient has multiple co-infections (no)
      5. Lyme always needs long-term antibiotics in everyone (no)
      6. Every patient with tick-borne disease has Lyme and every patient with Lyme has tick-borne disease (no)
   5. Stop the Assumptions!
      1. We must be very careful in data collection
      2. Use objective parameters
      3. Symptoms alone are nonspecific
         1. I still hear that night sweats mean Babesia
         2. Particular joint symptoms are not specific
      4. Symptoms alone don’t ensure causation of complex multi-symptom illness
      5. The field of chronic fatiguing illnesses is filled with assumptions
      6. Let’s stop such nonsense; the data from reliable labs will set you free
         1. Before starting a new lab, insist on split-samples to test validity of testing
         2. This is especially true for cash-only labs
      7. There are numerous lab abnormalities in Lyme that are due to the diffuse inflammation
   6. Definitions
      1. TGF β-1
      2. C4a
      3. C3a
      4. MMP9
      5. VEGF
      6. MARCoNS
      7. MSH
      8. VIP
      9. FoxP3 is a nuclear replication factor in CD4+ & CD25+ cells
         1. FoxP3 is made from FoxP0 which is
         2. Acted on by a kinase that sticks a phosphate on FoxP0 to make FoxP3
         3. Without FoxP3, the pathway of injury from CD4+ & CD25+ cells to pathogenic T-cells does not appear to occur.
         4. FoxP3 allows pathogenic T-cell formation but is also involved in stopping inflammation
         5. So if we fix Low CD4+ & CD25+ cells
            1. Including using elements like VIP to drive them up and…
            2. We block FoxP0 to FoxP3
            3. Will we have an additional way to block the cellular mechanism of inflammation?
            4. There are available kinase inhibitors that do exactly that
         6. The mechanism that converts FoxP0 to FoxP3 comes from the phosphatidyl-inositol 1,3 kinase pathway that’s linked to AKT
         7. These pathways are identified, active research is ongoing especially with P1, 3K and its role with AKT as an additional pathway of injury in these people with inflammatory processes suffers from.
      10. Innate immunity
      11. Ag detection
      12. Ag presentation
      13. Dendritic cells and Ag Processing; PAPC
      14. Ag Delivery
      15. CTLA 4
      16. Naïve T cells
          1. Cytotoxic Lymphocyte Factor 4 can block passage of an immune signal from a dendritic cell to a naïve T cell.
          2. This works by blocking the attachment of the naïve T cell to its -T cell receptor on the dendritic cell.
      17. B Cells
   7. Where Post-Lyme therapy *fails*
      1. Failure of adequate “30,000 feet”
      2. Water-damaged buildings lead the list
      3. MARCoNS is almost guaranteed if antibiotics have been used for longer than 1 month
      4. Ignoring the issues involving;
         1. AGA, ACLS, Actin auto-Ab’s
         2. ADH/Osmolality
         3. MMP9 untreated
         4. C3a not done
         5. C4a not done or wrong assay used
         6. TGF β-1 ignored
      5. If there is defective Ag presentation, is it reasonable to use a Lyme Ab test? (Yes)
   8. Failure of Post-Lyme Syndrome
      1. MSH & VIP deficiency
         1. Antibiotics will never fix this
      2. Ignoring T-reg cell physiology
         1. Antibiotics will never fix this in those with HLA susceptibility to Post-Lyme Syndrome
      3. Use of Ab testing in the face of HLA-DR associated failure of Ag presentation
      4. Assumption that “once Lyme, always Lyme”
         1. Lyme will change the host such that as time goes by, HLA susceptibility to other diseases will be expressed such that
         2. If Lyme was present last year, and they get sick again this year, do not assume that it’s due to Lyme again this year, what else can cause CIRS? Use your differential diagnostic skills!
         3. Don’t assume that this is a cyst phase, or co-infection that was latent
         4. Look at this as a new illness; it probably will be
      5. Does finding Borrelia burgdorferi in tissue mean causation of illness?
      6. Dr. Shoemaker mentions that he has atypical mycobacteria alive and reproducing in his lungs, does he have mycobacterial PNA due to granulomas in his lungs? No
      7. If there is a spirochete inside of a fibroblast, does that automatically mean Lyme? No
      8. Could there be sequestration of Lyme within granulomata? Possibly
      9. Currently we don’t have the lab tests and ability to look at all tissues
         1. If there’s a negative stain for Borrelia, it doesn’t mean no disease, it means we haven’t found disease, we didn’t get it at that time.
   9. Look for the final common pathway; Post-Lyme becomes inflammatory CIRS
      1. Abnormalities in innate immune responses (non-specific for cause)
         1. Exactly what it is in other etiologies for CIRS
         2. VCS (+) as from all other causes of CIRS
      2. Host response must be defined with labs
      3. Incredible amplification of multiple pathways follows initiation
      4. CIRS!
   10. [Biotoxin Pathway](http://www.survivingmold.com/docs/biotoxinpathwayritchieshoemakermd.pdf)
   11. Putting the [Biotoxin Pathway](http://www.survivingmold.com/docs/biotoxinpathwayritchieshoemakermd.pdf) to work
       1. 150 patients with confirmed Lyme
       2. 60% ECM rash (+)
       3. 32% IgG (+) Western Blot
       4. 74% IgM (+)
       5. Data recorded at baseline, after 3 weeks of oral antibiotics then after CIRS therapy
   12. Biotoxin Therapy
       1. Done after antibiotic therapy X 3 weeks
          1. Doxycycline for women (Amoxicillin causes to much vaginal candida)
          2. Doxycycline or Amoxicillin for men
             1. Very little Amoxicillin used
          3. If not 100% fine after antibiotics, they were set up for CIRS treatment
       2. Differential Diagnosis is negative
       3. Cholestyramine or Welchol for 30 days after
          1. Actos and no-amylose diet for 5 days if Leptin >7 or
          2. 2.4 EPA Omega-3 and
          3. 1.8 DHA if Leptin <7
          4. Reducing Leptin to <2, raises MSH production tremendously
          5. Ensure Leptin is at least <7
       4. Eradicate MARCoNS (BEG spray and Rifampin)
       5. Correct ADH/Osmolality (DDAVP)
       6. Correct Androgens (check Testosterone/Estrogen ratio)
       7. PAI-1
       8. Correct Anti-gliadens Abstinence from gluten if TTG (+)
   13. **C4a by Step**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **C4a base** | **C4a after abx** | **C4a after CIRS Rx** |
| Master | 9,336 | 6,797 | 2,533 |
| ECM Rash (+) | 8,025 | 6,912 | 2,643 |
| ECM (-) | 11,571 | 6,558 | 2,321 |
| IgG (+) | 6,795 | 6,154 | 2,215 |
| IgG (+) | 10,691 | 7,189 | 2,726 |
| IgM (+) | 9,753 | 6,656 | 2,797 |
| HLA (+) | 9,771 | 8,307 | 2,745 |
| HLA (-) | 8,348 | 4,011 | 1,512 |

* + 1. HLA doesn’t make much of a difference on whether the patient gets Lyme or not, but it does make a difference in duration of Lyme problems
    2. HLA non-susceptible patients do very well with CIRS therapy
    3. Antibiotics alone did not cure these patients
    4. CIRS therapy did cure these patients.
  1. **C3a by Step**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **C3a base** | **C3a after Abx** | **C3a after CIRS Tx** |
| **Master** | 638 | 233 | 126 |
| **ECM (+)** | 652 | 436 | 251 |
| **ECM (-)** | 627 | 443 | 321 |
| **IgG (+)** | 738 | 442 | 188 |
| **IgG (-)** | 587 | 434 | 273 |
| **IgM (+)** | 645 | 443 | 273 |
| **IgM (-)** | 620 | 427 | 245 |
| **HLA (+)** | 620 | 556 | 271 |
| **HLA (-)** | 674 | 296 | 212 |

* + 1. None of the numbers are >940
       1. None of these patients are being seen within the first 4-5 days of their illness
    2. As expected, there’s a good C3a reduction with antibiotics
       1. C3a forms with bacterial/spirochetal membranes being found in the blood stream.
    3. Further reduced C3a after Actos & Cholestyramine
    4. High C3a does not automatically mean Lyme, but it does fall with CIRS Rx
  1. **TGF** β-1 **by step**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **TGF** β-1 **Base** | **TGF** β-1 **after Abx** | **TGF** β-1 **after CIRS Rx** |
| **Master** | 7,378 | 8,538 | 3,149 |
| **ECM (+)** | 7,354 | 8,095 | 2,522 |
| **ECM (-)** | 7,415 | 9.335 | 2,350 |
| **IgG (+)** | 7,704 | 5.701 | 3.028 |
| **IgG (-)** | 7,252 | 9,484 | 3,194 |
| **IgM (+)** | 7,323 | 9,716 | 3,154 |
| **IgM (-)** | 7,568 | 5,594 | 3,135 |
| **HLA (+)** | 7,516 | 11,005 | 3,250 |
| **HLA (-)** | 7,063 | 3,331 | 2,141 |

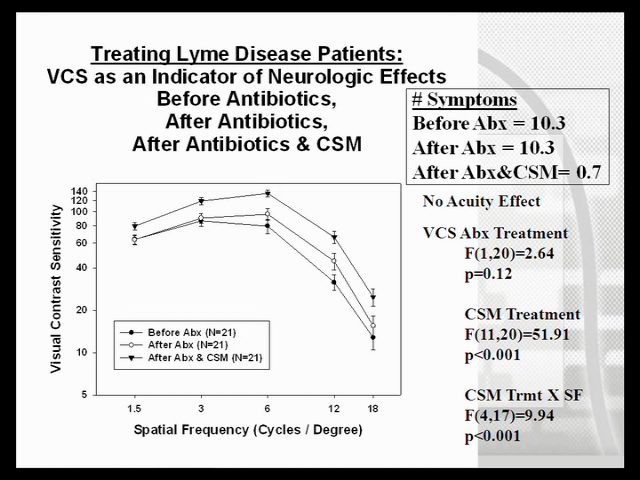
* + 1. No significant differences between ECM, IgG, IgM, HLA statuses at baseline
    2. Ideal cut-off is 2,380, this is only achieved in the bottom cohort HLA-
    3. How much longer should we continue straight biotoxin therapy?
       1. The table above does not include use of Losartan, VIP
       2. Dr. Shoemaker tends to ignore TGF β-1 as long as they’re <5,000
       3. Clinically, he has not seen problems from this approach.
       4. Further lowering can be attained with Losartan or VIP
  1. **MMP9 By Step;**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **MMP9 Base** | **MMP9 After Abx** | **MMP9 after CIRS Rx** |
| **Master** | 459 | 410 | 241 |
| **ECM (+)** | 465 | 350 | 255 |
| **ECM (-)** | 447 | 564 | 210 |
| **IgG (+)** | 549 | 342 | 228 |
| **IgG (-)** | 410 | 464 | 250 |
| **IgM (+)** | 426 | 416 | 219 |
| **IgM (-)** | 551 | 401 | 275 |
| **HLA (+)** | 427 | 504 | 264 |
| **HLA (-)** | 530 | 539 | 189 |

* + 1. No huge numbers
    2. Antibiotics don’t help much, some cohorts actually worsened with higher numbers
    3. This is no surprise with the recollection that MMP9 reflects ongoing inflammatory effects, being split from MMP14 from endothelial cells, macrophages and monocytes.
    4. After CIRS therapy, MMP9 drops beautifully as it should.
    5. There were no measurements of MMP9 at the conclusion of Actos when they would have been at their nadir.
  1. **VCS by HLA**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Base | After Abx | After Rx |
| **% Positive** | 98 | 68 | 0 |
| **% Negative** | 2 | 32 | 100 |
| **% Positive HLA Susceptible** | 97 | 96 | 0 |
| **% Positive HLA Non-Susceptible** | 100 | 15 | 0 |

* + 1. VCS is not 100%
       1. 8% of the negative patients who were sick got better with treatment
       2. They further improved after antibiotics with CIRS therapy
       3. So VCS by itself can be negative.
    2. Of the proportion with VCS (-), there is a disproportionate number of teenaged women
    3. Of the men and the older VCS (-) patients, there are artists, photographers, baseball players, and interior designers.
    4. He doesn’t stop the CIRS Rx until the VCS is fixed;
       1. He monitors VCS as well as all of the other lab parameters, most of which improve before VCS normalizes.
    5. HLA Susceptible patients will NOT have VCS improve with antibiotics.
       1. The improvement after abx comes from the group that is not HLA susceptible
    6. Let the VCS guide your therapy, treat until there is a VCS plateau.
       1. Some rare folks will never have a fully normalized VCS.
  1. Treating Lyme Patients with VCS as an indicator of neurologic effects



* + 1. Before antibiotics
    2. After antibiotics
    3. After antibiotics & Cholestyramine
  1. CIRS Therapy
     1. Think about immunological illnesses
     2. Think sepsis (versus bacteremia)
     3. Think about Th-1, Th-2, and Th-17 (Th-9!))
        1. More is being learned about Th-17 in immunology journals
        2. Currently, there is no commercially available lab test to assess Th-17 cell level and/or activity
        3. Th-9 is a brand-new player in the field
     4. Think about capillary hypoperfusion
     5. Think about loss of neuropeptide control of peripheral inflammation
     6. Don’t forget coagulation!
     7. The complexity of the immune response does not mean that we have the luxury of not treating what we now know.
     8. Activation of C4a; (C3a only if bacterial membrane platform is present.)
     9. TGF β-1 is the gorilla here
     10. We need to look at T-regulatory cells if TGF β-1 is increased
     11. T-reg’s are low in Post-Lyme
     12. Raising CD4+ CD25+ FoxP3?
  2. CD4+ CD25+ FoxP3+
     1. Hot in immunology; inducible (i) cells
     2. High TGF β-1 increases T-Reg cells (i) that should suppress inflammatory responses, including auto-immunity
     3. But the highest TGF β-1 is in auto-immune illness
     4. If FoxP3 split off in inflamed tissue pathogenic T cells and more TGF β-1
     5. High levels of CD4+ CD25+ & FoxP3+ cells should be suppressing inflammation.
        1. Yet, in autoimmunity is where you find some of the highest levels of TGF β-1
        2. We need additional definition as to why the CD4+ and CD25+ convert to pathogenic T-cells in inflamed tissue
     6. Hopefully, in the future, we’ll find that interventions that increase the T-Reg cells will help our Post-Lyme patients
  3. T-Reg’s dominate Post-Lyme
     1. Interventions to increase T-reg?
     2. Drop Pathogenic T-Cells
     3. What if the TGF β-1 is blocked?
        1. No rise in T-reg (i)
        2. No rise in TGF β-1 from pathogenic T cells generated in situ
        3. This stops the feed-forward amplification loop
     4. Problem appears to be solved by stopping TGF β-1!
     5. Newly discovered kinase inhibitors may hold the answer.
  4. T-Reg’s are plastic;
     1. If FoxP3 added to CD4+ CD25+ cells is needed for suppression of local inflammation (it is) and that induction is driven by TGF β-1 (it is) and then FoxP3 is split off in inflamed tissues (it is) and then FoxP3 negative cells turn on more TGF β-1 (it does), why wouldn’t stopping TGF β-1 work? (It does)
     2. *So TGF β-1 starts inflammation, FoxP3 stops inflammation*
     3. Stopping TGF β-1 stops inflammation
     4. Interventions that raise the CD4+ and CD25+ activity should help stop auto-immunity even more than what we see in Lyme.
  5. Before the leap to T-reg
     1. What do we know about who gets Post-Lyme Syndrome?
     2. What do Post-Lyme people have?
     3. Is the T-reg and TGF β-1 problem unique to Lyme Patients
        1. Nope; just about every biotoxin person has it, like CD-57
        2. CD-57 cells are not unique to Lyme as some investigators once thought; it goes up with mycotoxins too.
     4. This is an emerging field.
  6. Innate Immunity; is it old? No
     1. System of Ag detection and response is over three billion years old
     2. Evolutionarily conserved in mice, men, sea squirts, slime molds and nasturtiums
     3. Look what came first; blue green algae, fungi, Dinoflagellates, spirochetes
     4. 1989 CSH Symposium; Janeway
     5. 1985 First TNF paper; 50,000 more papers in the last 10 yrs.
     6. The intra-cellular parasites are incredibly well adapted for life inside of a host cell.
        1. They have their own nuclear DNA
        2. They have their own mitochondria DNA
        3. They have their own 3,200-kilodalton-plasmid ring that codes for enzymes necessary in the dark phase of photosynthesis.
        4. Some early papers on the Rx of malaria included use of Atrazine; a herbicide
        5. Horses with sarcocystis are given a drug called Marque; another herbicide
     7. These diseases can up-regulate or down-regulate each other
        1. Lyme down-regulates Babesia
        2. These organisms each make their own toxin Eg.
           1. Malaria (GPI)
     8. To treat these diseases it is necessary to kill
        1. Nuclear DNA
        2. Mitochondrial DNA
        3. Plasmid plant-source DNA of ATPases as well
        4. It’s also necessary to knock out their toxins with Welchol and Cholestyramine
     9. Horses and dogs are afflicted by these organisms
     10. We probably will never be able to treat humans with herbicides despite massive “informed consent”

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1. **Review of Post-Lyme Syndrome**
   1. Let’s not forget genetics
      1. Learn HLA DR by PCR (SSOP)
         1. A DNA-selective assay
      2. Look for 4-3-53 (0401, worst of 12)
      3. Look for 11-3-52G (this one is easy)
         1. Long arms, long fingers, flexibility
      4. The “dreaded”
         1. Worst TGF β-1
         2. Most abnormalities
   2. Lyme HLA DR Relative Risk >2 (Lyme RR is a bit different from mycotoxin RR)
      1. 21% of the normal population
      2. 4-3-53; 11-3-52B; 14-5-52B
      3. 15-6-51 and 16-5-51
      4. Post-Lyme in 20-25% of the population
      5. Antibiotics alone won’t help here
      6. Our data (N+1,200) show Post-Lyme almost never occurs in other HLA’s.
   3. Do certain HLA haplotypes have worse inflammation in Post-Lyme?
      1. You bet!
      2. 2003 Shoemaker et al
      3. 2006 Steere (JEM)
         1. 4-3-53
         2. 11-3-52B
         3. 15-6-51
         4. 116-5-51
   4. Biotoxins
      1. VERY small molecules (usually carried by glycoproteins, bind to receptors on dendritic cells and elsewhere).
      2. Ionophores; pass cell to cell
      3. Inflammagens bind to receptors;
         1. Toll; Mannose
         2. Ficolins; C-linked lectins
         3. Have predictable inflammatory results
      4. Direct neurotoxicity
      5. Defective Ag presentation
   5. Positive-Feedback Loops
      1. HLA DR inhibition/withdrawal (IL-10) from surface of macrophages/Ab production
      2. Bordetella and Anthrax block Lysosome/ER complex
      3. Increasing TGF β-1 leads to T-reg cell dysfunction forming pathogenic T-cells
      4. Differential gene activation (genomics to the rescue, we hope!!)
      5. Currently, CD4+ CD25+ FoxP3+ dysregulation is front and center for research.
   6. Antibiotics don’t fix innate immunity
      1. Interestingly however, both Doxycycline and Macrolides have some intrinsic anti-inflammatory properties
         1. There are even patients with multiple sclerosis being treated with Doxycycline
         2. 15-6-51 is an HLA risk factor for MS
      2. Lyme, Mold & MS all lower T-Reg cell counts
         1. Treatment currently is somewhat nonspecific in attempts to drive up T-Reg cell counts.
      3. Babesia is horribly over-diagnosed but activates innate immunity
         1. Look for smear; hemolysis
         2. Look for low haptoglobins
      4. Bartonella diagnosis is so flawed now
      5. Ehrlichia persistence? Confirm?
   7. Diagnosis is not just exclusion
      1. Chronic, multisystem, multisymptom illness refractory to all interventions
      2. Dense innate immune abnormalities are invariably present
      3. Genetic basis (HLA DR by PCR)
      4. Onset isn’t the end of the diagnosis
      5. Ongoing effect of environmental exposures needs to be remembered;
         1. Don’t Forget To Ask!
   8. Shoemaker’s Treatment Message;
      1. Look for environmental exposures and repeat of it first and foremost!
      2. Establish a decent baseline of results of innate immunity testing
      3. Look for and eradicate biofilm formers
      4. Treat the inflammatory physiology
      5. What do you have left?
      6. What happens when the injured patient is exposed next week?
         1. Repeat illness
         2. Always be on the lookout for repeat exposures!
         3. Sicker Quicker
   9. What you need to know:
      1. Symptoms must be present
      2. Get the VCS
      3. Labs must be present to show what is and what is not
      4. DDx must be there.
      5. The labs will show you the way;
         1. Start looking at innate immunity as a target
         2. Start looking at targets you can fix
         3. Fix the targets; watch the illness disappear
         4. Wait for relapse

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1. **Post-Lyme Syndrome Case Reviews**
   1. Case Review #1
      1. Laundry clerk shows you her ECM rash, 3 days old, few symptoms
      2. You demand labs and won’t just give her the antibiotics that she requests
      3. HLA DR 4-3-53 (0401)
         1. TGF β-1 17,598
         2. C4a 8,705
         3. C3a 1,284
         4. MMP9 739
      4. Her friend the hairdresser says it’s not Lyme
      5. Send her a certified letter; she takes no Abx (the letter is his CYA)
      6. 3 months later she is Dx’ed with “fibromyalgia”, alopecia universalis and vocal cord polyps (and nasal polyps are both caused by TGF β-1) (not the case with colon polyps)
      7. She has pretty typical TGF β-1 (catagen hairs; Transformation!!)
         1. Growing hair follicles are anagen
         2. Rest-phase hair is telogen
         3. Dying hair follicles are catagen due to TGF β-1
            1. Dermatologists and others discussing “hair loss” never mention the effect of TGF β-1
      8. One year later has restrictive lung disease
   2. Case Review #2
      1. 59 wm Farmer; 15-6-51 and 7-2-53
      2. Wife had ECM (+) Lyme X 3
      3. Presents for evaluation of knees and hands; all inflamed, Tap (-) no C4a in joint fluid (C4a is not a good marker in CSF)
      4. ANCA (anti-neutrophilic cytoplasmic antibody) (+) Atypical; no Ulcerative Colitis or Cirrhosis
      5. TGF β-1 high, C4a high, C3a Normal, MMP9 837
      6. Given antibiotics as the exposure was only 3d old
      7. After 1 month on Abx not improving
      8. TGF β-1 doubles, MMP9 climbs to 1,329, C4a doesn’t fall, C3a still normal, Lyme Western Blot negative
      9. Starts Actos and Cholestyramine 1 month later slightly better
         1. MMP9 312
      10. Starts Erythropoietin 8,000 units twice/week for 5 doses
          1. C4a normalizes
      11. Then given Losartan 25 mg bid X 6 months
      12. TGF β-1 normalizes
          1. Joint symptoms abate
          2. ANCA converts to normal
      13. Didn’t need VIP, Losartan was well tolerated
          1. And Losartan is much less expensive than VIP!
   3. Case Review #3
      1. Mold inspector with remote history of only 4 bands Lyme in CSF, Rx’ed with oral abx
      2. Was well until 2004 MRI with contrast, does OK for a few years after Gadolinium exposure
      3. Now skin thickening similar to scleroderma, Multiple symptoms, looks like Parkinson’s
      4. Had long-term esophageal problems/dysmotility
      5. Might have had another tick bite
      6. VCS (+)
      7. Another physician had treated him with Cholestyramine which didn’t help at all
      8. Lung diffusion capacity abnormal
      9. All auto-immunity studies were negative/wnl despite looking like he has scleroderma
      10. Could he have ongoing mold exposure?
      11. Went back on Cholestyramine and had his home remediated
      12. VCS Normalized but patient is still ill
      13. Losartan provides a ray of hope
      14. 3 months later skin is clear, Parkinson’s is gone
      15. Was this Lyme, Mold or Gadolinium?
      16. Overall, the culprit was probably TGF β-1 causing endo- to epithelial mesenchymal transformation.
          1. It changed his cell types.
      17. Sebhorreic keratosis’, Actinic keratosis’ will often appear at about the same time TGF β-1 is elevated
          1. TGF β-1 changes cell types!
   4. Case Review #4
      1. Virginia Beach Pre-teen
      2. Unequivocal diagnosis of Multiple Sclerosis had plaguing on her CNS MRI
      3. Oligoclonal bands; demyelination
      4. Rx for Lyme; had 3 bands in CSF
      5. Rx steroids for vision compromise, then another physician treats for Lyme with partial improvement
      6. Parents defer MS Rx (Betaseron)
      7. Patient finally comes in to see Dr. Shoemaker
      8. What’s missing?
      9. ERMI 10, moldy junction of garage to home
         1. HVAC spreads bioaerosols
      10. Cholestyramine started. Symptoms did not intensify, so probably not Lyme
          1. TGF β-1 >40,000
      11. Neuro stabilizes, home remediated
      12. F/U TGF β-1 <3,000; CNS lesions melt
      13. Neurology wants her to stay on long-term Cholestyramine
   5. Case Review #5
      1. Documented ECM rash X 10, HLA 15-6-51
      2. Won’t use Permethrin
         1. Tip; go to farm supply store, get 10% Permethrin for horses, take 1 oz., add to 31 oz. water, put it in a water-mister/spray bottle
      3. Daughter with psoriasis corrected by Actos and then maintained on Enbrel
         1. Actos also lowers TNF
      4. Cholestyramine, antibiotics help; on Amoxicillin, Erythropoietin, Losartan and VIP were of no help
         1. On Amoxicillin bid long-term due to constant tick exposure
      5. Given Methotrexate, then Prednisone, then VIP again
         1. He had gone beyond what VIP was able to fix due to ongoing Lyme re-exposure
      6. CD4+ CD25+ was 7, now 48 after starting Methotrexate so he improved
      7. vWF Ag and Ristocetin associated co-factor >250!
      8. IV Rocephin🡪Clotted off his PICC line
      9. Had a Mediterranean Recluse spider bite, Mold (Aspergillus) as well, then a profound illness after eating grouper in Key West
   6. A word on Recluse Spiders
      1. Like Babesia, is over-diagnosed
      2. Mediterranean is here, not brown recluse
         1. Look at the gonads to tell the difference
      3. Bite site is a reservoir for toxins
      4. CIRS; Rx Cholestyramine, Actos, Topical Cholestyramine
      5. Follow IL-1b and TGF β-1
      6. Same Rx for Mycobateria invadens (Buruli ulcer, mycolactones)
      7. Same illness in Chesapeake Bay on rockfish, not M. invadens, now, M. pseudoschatzii is infecting the bay’s rockfish.
   7. Case Review #6
      1. 14 yo girl from Fairbanks AK
      2. Home is super-tight insulated
      3. Moisture intrusion is absence of exit
      4. Overweight, Hirsute, CFS
      5. Has seen 20 physicians without relief; ELISA Lyme negative
      6. MD suspects mold/no ERMI done
      7. Had been given Rx for Cholestyramine without much relief
         1. VCS (+)
         2. HLA 15-6-51 and 4-3-53
         3. Leptin 80
         4. Androgens high (probably had PCOS)
         5. MSH low
         6. Lyme Western Blot (WB) (+) IgM
         7. Home ERMI (-1)
         8. Rx; Doxycycline X 3 weeks, she is fine now, has lost 40 lbs. on Actos
         9. Next school she’s due to attend is a WDB
   8. Case Review #7
      1. NJ 50 WM central vision loss since MD witnessed ECM Rash
      2. CSF negative, no help with IV Abx for months
      3. Saw all of the best Neuro-opth’s around
      4. 11-3-52B, still flexible, long fingers
         1. C4a elevated
         2. C3a normal
         3. TGF β-1 15K
         4. MARCoNS (+)
         5. VIP undetectable
      5. Started Actos and Cholestyramine
      6. Home ERMI is >15, is remediated
      7. Treated for MARCoNS, re-cultured at patient’s request, started VIP
      8. MARCoNS still present but a different organism, reservoir unknown, Re-Rx with BEG spray
      9. Calls a month later (1/17/11)
         1. No more paresthesias in feet and hands
         2. Fatigue has resolved
         3. Headache has resolved
         4. Gold is now visible as gold
         5. Sun is bright yellow
         6. Reds that were brown are now red
         7. Neuro-ophth will re-evaluate him
      10. Case isn’t over, still central visual loss, due to have re-evaluate in 6 months
   9. A word on Coagulase
      1. PAI-1 (Plasminogen Activator Inhibitor) is raised in innate immunity PAI-1 is a big player in innate immunity
      2. Rx; with Actos and no amylose diet
      3. vWF profile is critically important
      4. If there is mucosal bleeding, look for acquired vWF (low Ristocetin and low multimers); Rx DDAVP (which can resolve it in an hour) (from high C4a)
      5. Don’t forget ACLA cardiolipin
         1. If clotting is likely, Coumadin (heparin’s a pain)
      6. Avoid dehydration if clotting is a concern; it accelerates the clotting.
   10. A word on XMRV
       1. Barely a year since publication
       2. To much controversy  
          Lots of conflict of interest
       3. Norway site shows no difference in labs if (+) or (-) serology/culture
       4. Lots of different viruses have been postulated for CFS
       5. No; p30, p31 is not XMRV
   11. VCS is so easy!
       1. Office/bedside screening
       2. Non-invasive
       3. Low cost
       4. Reproducibly reliable
       5. 50 year track record
       6. Under-used
   12. Ciguatera
       1. CIRS
       2. Genomics are known and defined
       3. Perhaps best defined biotoxin illness in the literature for over the past 60 years
       4. Symptoms no different from post-Lyme

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1. **Attendee Questions**
   1. Suggestion to use a lint-roller/adhesive after being in areas with tick infestation to hopefully remove ticks that haven’t yet locked on
   2. Suggestion that Major League Baseball consider monitoring VCS’s on their pro’s
      1. VCS’s are so quick, easy to do and inexpensive, they should probably be used to screen EVERYBODY, we’d probably pick up a lot more morbidity from CIRS that could be fixed to improve lives.
   3. Re; Macular Degeneration and VCS;
      1. Research is being done on VCS and MD
      2. Erythropoietin can help clear up MD via Neuro-remodeling of the retina.

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1. **Physician's Order Sheet** (Updated 8/31/2011)
   1. Specimen Requirements

* 1. [Chart Draw Sheet](http://www.tequestafamilypractice.com/articles/CIRSLabs.xlsm) [**(** **Lab Summary)**](#XXISummaryofLabs)

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1. **Summary of Immuno-Specific Lab Tests** [**(** **Lab Summary)**](#XXISummaryofLabs)**;**
   1. C4a Normal Range: 0-2,830 ng/ml
      1. C4a has become the inflammatory marker of greatest significance looking at innate immune responses in those with exposure to Water Damaged Buildings (WDB).
      2. The complement system is a group of proteins that move freely through the bloodstream. The proteins work with your immune system and play a role in the development of inflammation.
      3. Each complement activates inflammatory responses, with spillover of effect from the innate immune response to acquired immune response and hematologic parameters.
      4. These short-lived products are re-manufactured rapidly, such that an initial rise of plasma levels is seen within 12 hours of exposure to biotoxins, and sustained elevation is seen until definitive therapy is initiated.
   2. TGF β-1 - Transforming Growth Factor β-1 Normal Range: <2,380 pg/ml
      1. TGF β-1 is a protein that has important regulatory effects throughout innate immune pathways. This protein helps control the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (motility), and the self-destruction of cells (apoptosis). The TGF β-1 protein is found throughout the body and plays a role in development before birth, the formation of blood vessels, the regulation of muscle tissue and body fat development, wound healing, and immune system function (especially regulatory T-cells).
      2. TGF β-1 can impair T-regulatory cell function, which in turn contributes to the activation of autoimmunity, yet TGF β-1 also plays a role in suppressing autoimmunity (!). TGF β-1 has become important in the exploding incidences of childhood asthma, raising the tantalizing issue of remodeling due to biotoxin exposure. The EPA says that 21% of all new cases of asthma are due to exposure to Water Damaged Buildings. If an individual develops wheezing after exposure to water damaged buildings, look for remodeling to be the cause. Remodeling means "something" happens that the airway changes to be more reactive and in need of medications to reduce wheezing. Neurologic, autoimmune and many other systemic problems also are found with high TGF β-1
      3. LabCorp; 905036 Frozen Plasma Lavender EDTA sent out by LabCorp
   3. MSH - αMelanocyte Stimulating Hormone Normal Range: 35-81 pg/mL
      1. Alpha α melanocyte stimulating hormone (αMSH) has multiple anti-inflammatory and neurohormonal regulatory functions, exerting regulatory control on peripheral cytokine release, as well as on both anterior and posterior pituitary function.
      2. In mold illness, αMSH will be too low in over 95% of patients. This means increased susceptibility to mold illness, ongoing fatigue, pain, hormone abnormalities, mood swings, and much more. αMSH is a hormone, called a regulatory neuropeptide, and it controls many other hormones, inflammation pathways, and basic defenses against invading microbes. Without αMSH, bad things happen; chronic sleep disorders with non-restful sleep develop, and endorphin production is reduced, so chronic pain follows.
   4. VIP - Vasoactive Intestinal Polypeptide Normal Range: 23-63 pg/mL
      1. Vasoactive intestinal polypeptide (VIP) is a neuroregulatory hormone with receptors in the hypothalamus. This hormone/cytokine regulates peripheral cytokine responses, pulmonary artery pressures, and inflammatory responses throughout the body.
      2. Low VIP levels are present in mold illness patients. This leads to unusual shortness of breath, especially in exercise. To date, every multiple chemical sensitivity patient Shoemaker has seen (over 500) have had low VIP. VIP plays a role similar to MSH in regulating inflammatory responses.
      3. With respect to the digestive system, VIP seems to induce smooth muscle relaxation (lower esophageal sphincter, stomach, and gallbladder), stimulate secretion of water into pancreatic juice and bile, and cause inhibition of gastric acid secretion and absorption from the intestinal lumen, which can lead to chronic, watery diarrhea.
      4. VIP replacement, when used according to a strictly administered protocol, has proven to be fabulously effective in returning chronically fatigued patients back to a normal life. Do not use VIP if you are exposed to mold (with ERMI values greater than 2); if you fail a VCS test; or if you have a MARCoNS present in your nose.
   5. MMP-9 Normal Range: 85-332 ng/mL
      1. Matrix metallopeptidase 9 (MMP-9) is an enzyme that in humans is encoded by the MMP9 gene. Proteins of the MMP9 family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes.
      2. It has been implicated in pathogenesis COPD by destruction of lung elastin, in rheumatoid arthritis, atherosclerosis, cardiomyopathy, and abdominal aortic aneurysm.
      3. MMP-9 delivers inflammatory elements of blood into subintimal spaces, where further delivery into solid organs (brain, lung, muscle, peripheral nerve and joint) is initiated.
      4. LabCorp; 500124 frozen serum gel barrier tube then transport to plastic transport tube prior to freezing
   6. Leptin Normal Range: Male: 0.5-13.8 ng/mL; Female: 1.1-27.5 ng/mL
      1. Leptin turns on how tightly the body holds onto fatty acids. When *Leptin is high*, one holds onto fatty acids and *stores* them in *fat.* This leads to rapid weight gain, and because of the high Leptin, standard approaches to weight loss like eating less and exercising more will fail. The inflammatory responses that causes Leptin levels to rise lead to patients who are chronically tired, in chronic pain, and forever overweight.
   7. ADH/Osmolality Normal Range: ADH - 1.0-13.3 pg/ml; Osmolality - 280-300 mosmol
      1. Antidiuretic hormone (ADH), or vasopressin, is a substance produced naturally by the hypothalamus and released by the pituitary gland. The hormone controls the amount of water your body removes.
      2. Osmolality is a test that measures the concentration of all chemical particles found in the fluid part of the blood.
      3. Symptoms associated with dysregulation of ADH include dehydration, frequent urination, with urine showing low specific gravity; excessive thirst and sensitivity to static electrical shocks; as well as edema and rapid weight gain due to fluid retention during initial correction of ADH deficits.
   8. ACTH/Cortisol Normal Range: ACTH - 8-37 pg/mL; Cortisol - a.m. 4.3-22.4 / p.m. 3.1-16.7 μg/dL
      1. ACTH is a hormone released from the anterior pituitary gland in the brain. Cortisol is a steroid hormone produced by the adrenal cortex, which is the outer part of the adrenal gland. The adrenal glands are located on top of both kidneys.
      2. Early in the illness, as MSH begins to fall, high ACTH is associated with few symptoms; a marked increase in symptoms is associated with a fall in ACTH. Finding simultaneous high cortisol and high ACTH may prompt consideration of screening tumors, but the reality is that this dysregulation usually corrects with therapy.
   9. ACLA IgA/IgG/IgM Normal Range: IgA - 0-12; IgG 0-10; IgM 0-9
      1. Anticardiolipins (ACLA) are autoantibodies. Antibodies are proteins in the blood that the body produces to fight off foreign agents. Antibodies do this by creating immunity against unfamiliar microorganisms. Autoantibodies are antibodies that are directed against one's self. They interfere with the normal function of blood vessels and react with proteins in the blood that are bound to [phospholipid](http://www.tequestafamilypractice.com/articles/MCSOverview.htm#EssentialFattyAcids) , a type of fat molecule that is a part of the normal cell membrane.
      2. IgA, IgM, and IgG are autoantibodies often identified in collagen vascular diseases such a lupus and scleroderma, and are often called anti-phospholipids.
      3. An increased risk of spontaneous fetal loss in the first trimester of pregnancy is not uncommonly seen in women with the presence of these autoantibodies. They are found in over 33% of children with biotoxin-associated illnesses.
   10. AGA IgA/IgG Normal Range: 0-19
       1. Antigliadin (AGA) antibodies are produced in response to gliadin, a small protein that is part of gluten, biologically active in wheat, barley and rye. These antibodies were thought at one time to be specific for Celiac Disease.
       2. Within 30 minutes of ingestion of gliadin, for those with antigliadin antibodies, there will be an inflammatory response. This inflammatory response can provide many symptoms, including some that mimic attention deficit disorder. We all know that some kids are labeled as having ADHD because of their abnormal behavior seen within 30 minutes of eating a cupcake. It is not the sugar in the icing; it is the gluten in the cake. Antigliadin antibodies are found in over 58% of children with biotoxin-associated illness.
   11. VEGF Normal Range: 31-86 pg/mL
       1. Vascular endothelial growth factor (VEGF) is a substance made by cells that stimulates new blood vessel formation and increases blood flow in the capillary beds. VEGF is a polypeptide. Deficiency of VEGF is quite common and is a serious problem in biotoxin illness patients that must be corrected. If you don’t have blood flow, cells begin starve and don’t work properly.
   12. CD4+CD25+; Regulatory T-Lymphocytes
       1. Help regulate the immune system to stop inflammation once the need has resolved
       2. LabCorp \*\*
          1. CD4+ 505008 Whole blood lavender and yellow ACD tube
          2. CD25+

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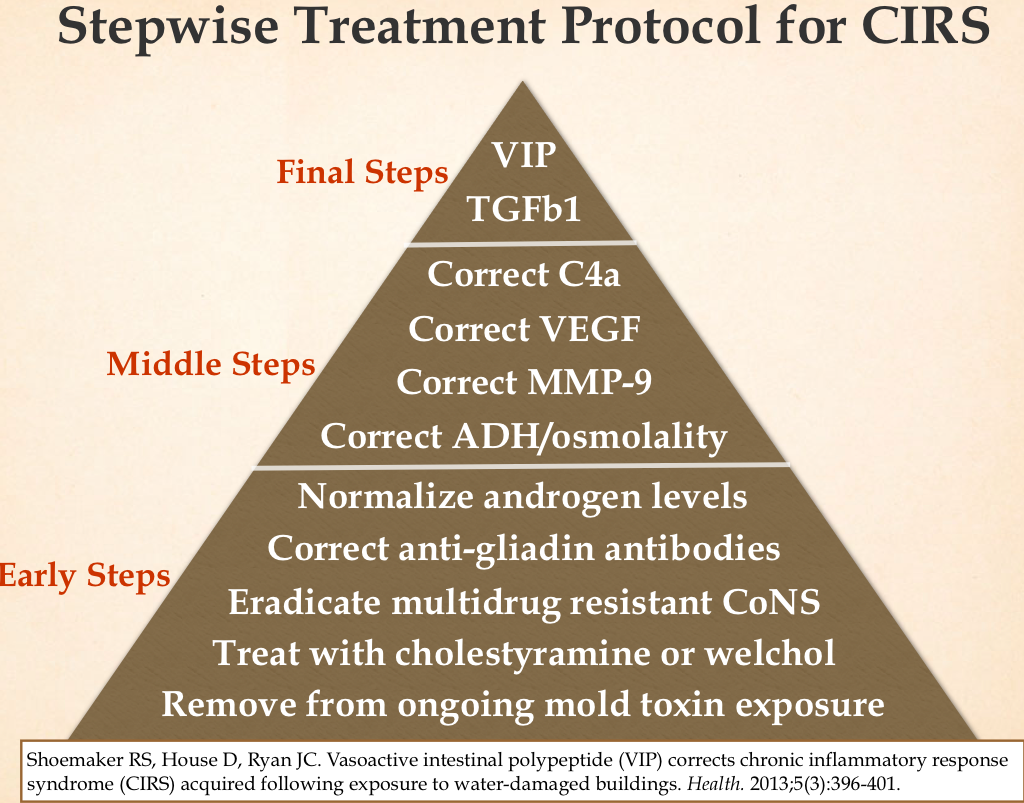
1. **Patient History; clues to CIRS**
   1. Anything that causes increased cytokine release; (Screen with [VCS Test](http://www.survivingmold.com/store1/online-screening-test))
      1. WDB’s/mycotoxins most commonly (ERMI)
      2. Post-Lyme syndrome (be careful of this; [Lyme Profile](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=6646))
      3. Ciguatera (under-diagnosed)
      4. Cyanobacteria (usually, but not always due to tropical fresh water)
      5. Pfiesteria (fish kills, “red tide”)
      6. *Recluse Spider* bites with central ulceration (rare)
      7. Infectious mononucleosis ([Mono Screen](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=654))
      8. Gardasil (by History)
      9. “Fibromyalgia” (Dx of exclusion, consider [mitochondrial disorders](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=90404), [Carnitine deficiency](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=70107), [abnormal fatty acid metabolism](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=90559), etc.)
      10. Lyme disease or vaccine
      11. Mononucleosis/EBV ([Mono Screen](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=654), [Epstein-Barr IgM Nuclear Ag](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=8426))
      12. [XMRV](http://en.wikipedia.org/wiki/XMRV) ([autism](http://en.wikipedia.org/wiki/Autism), [fibromyalgia](http://en.wikipedia.org/wiki/Fibromyalgia), [multiple sclerosis](http://en.wikipedia.org/wiki/Multiple_sclerosis), [amyotrophic lateral sclerosis](http://en.wikipedia.org/wiki/Amyotrophic_lateral_sclerosis), and [Parkinson's disease](http://en.wikipedia.org/wiki/Parkinson%27s_disease), [systemic lupus erythematosus](http://en.wikipedia.org/wiki/Systemic_lupus_erythematosus))
      13. [HIV](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=37708)
      14. Coxsackie ([Coxsackie A](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=37477), [Coxsackie B](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=7656)) (RNA enteroviruses)
      15. [Enterovirus](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=91811)
      16. [Kawasaki’s disease](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=5427) (mucocutaneous lymph nodes and coronary granulomas)
      17. Pneumovax (by history)
      18. Yellow jacket stings
      19. Any other event that causes [cytokine release (Eg. MMP9)](#MMP9)
   2. *Biotoxin Symptoms*
      1. Fatigue (MSH, TSH, CBC, VIP, Ciguatera exposure, [Mono Screen](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=654), [Lyme Profile](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=6646), [Epstein-Barr IgM Nuclear Ag](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=8426), [Coxsackie A](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=37477), [Coxsackie B](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=7656), [Enterovirus](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=91811), [mitochondrial disorders](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=90404), [Carnitine deficiency](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=70107), [abnormal fatty acid metabolism](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=90559), ACTH/Cortisol, etc.)
      2. Weak
      3. Aches ([ANCA](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=70171))
      4. Cramps (ADH, Osm, Cortisol, ACTH)
      5. Unusual sharp, claw, electrical pains (ADH/Osm/Lactate)
      6. Light sensitivity (MSH)
      7. Red eyes
      8. Blurred vision
      9. Tearing
      10. SOB ([ACE](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=683), VIP)
      11. Cough ([ACE](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=683), Pfiesteria)
      12. Sinus symptoms (MARCoNS)
      13. Abdominal pains (AGA, MMP9)
      14. Secretory diarrhea (AGA, Pfiesteria)
      15. Morning stiffness (ESR, MSH)
      16. Arthritis (ESR, MMP9, ANA, RF)
      17. Executive and Cognitive dysfunction (hold the neurocognitive testing, take an exposure history, Pfiesteria provided a great platform to demonstrate when testing in hyperacute and recovery periods were done in cohorts. (VIP, VEGF, MSH
          1. Decreased recent memory
          2. Difficulty concentrating
          3. Word-finding difficulty
          4. Decreased assimilation of new knowledge
          5. Confusion
          6. Disorientation in familiar places
      18. Memory loss (Pfiesteria, MR-Spectroscopy)
      19. Impaired concentration ([Lyme Profile](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=6646))
      20. Trouble swallowing
      21. Assimilation problems
      22. Confusion
      23. Disorientation
      24. Impaired mood (MSH)
      25. Impaired appetite (MSH, Leptin)
      26. Sweats/chills; thermoregulation problems
      27. Frequent urination (ADH, Osm)
      28. Excessively thirsty (ADH, Osm)
      29. Spontaneous abortions/prior diagnosis of Cardiolipin Antibodies (MSH also does this)
      30. Electrical shock sensation when touching skin (ADH, Osm)
      31. Paresthesias/numbness, tingling (Ciguatera?)
      32. Altered taste (Ciguatera?)
      33. Tremor
      34. Vertigo/dizziness
      35. Menstrual/Menopause/impaired libido (MSH, sex-steroids)
      36. Bleeding/bruising ([vWF](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=19790))
      37. Thrombosis ([Cardiolipin panel](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=36333))
   3. Physical findings;
      1. Not very helpful…
      2. Patient may have mild tremor, low grade tachycardia etc.

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1. **At-A-Glance CIRS Management;** [**K Berndston MD**](http://www.slideshare.net/keithberndtson/mold-toxicity-syndrome-cirs)



1. [**Stepwise Treatment Protocol for CIRS**](http://www.slideshare.net/keithberndtson/mold-toxicity-syndrome-cirs)



* 1. **Labs** [**(** **Lab Summary)**](#XXISummaryofLabs)**;**

|  |  |  |
| --- | --- | --- |
| **Abnormality** | **Symptoms** | **Intervention** |
| Symptoms suggest CIRS? |  | [VCS Test](http://www.survivingmold.com/store1/online-screening-test) |
| VCS Abnormal? |  | [ERMI Testing; (732) 355-9018](http://www.mycometrics.com) |
| ERMI Abnormal? |  | **STOP ALL EXPOSURE!** [Check HLA DR1/3/4/5 DQ](http://www.tequestafamilypractice.com/articles/CIRSLabs.xlsm) |
| [HLA at risk?](http://www.tequestafamilypractice.com/articles/CIRSHLA.htm) **Labcorp:** ACC 20001604256 HLA DRB, DQ Typing |  | [Cholestyramine](#Cholestyramine) and [Nasal Culture for MARCoNS](https://www.dxos.com/mold-illness-testing/) Treat until VCS normalizes |
| [Evaluate Pt. History of CIRS Risks](#PMHCluestoCIRS) |  | [Order Initial Labs considering patient’s risk history](file:///F:\Dropbox\woundedhealersnc\Gov%20McCrory\Physician%20Wellness%20LLC\CAM\CIRS\Chart%252525252520Draw%252525252520Sheet%252525252520Macro-Enabled%252525252520Workbook.xlsm) |
| MARCoNS (+)? |  | [Begin BEG Nasal Spray](http://www.rxandhealth.com) & Rifampin 300 mg 2 tabs/d |
|  MMP9, PAI-1, Leptin, C3a, C4a, & TGF β-1;  MSH, (VEGF & VIP will also be low, respond to different Tx) | C/W CIRS | Actos/Low Amylose Diet (Omega-3’s if Leptin <7) |
|  TGF β-1 | Causes problems in lungs, autoimmune, Neuro (tremor, learning disability, MS, TM) (need chilled tubes) | Losartan, exp3179 (experimental) or VIP |
| If  AGA, gluten free and check Tissue Trans-glutaminase | 1st manifestation of autoimmunity, grain intolerance | Gluten free X 3 months, then recheck |
|  MMP9/ADH-Osm/ Androgens can all be lumped together | As noted above/below | Actos/low amylose diet (Omega-3’s if Leptin <7) |
| ADH/Osm | Thirst, skin shocks | DDAVP nasal/monitor  Na |
| Leptin | Obesity, DM | Improves with CIRS Tx , can  VIP, MSH |
| MSH | Sleep disturbances, chronic pain, enthesopathy, GI/malabsorption, leaky gut, prolonged illness, resistant Staph, Pituitary/Adrenal axis disruption, Reduced sex hormones, reduced ADH | Due to low Leptin activity on Hypothalamus (Leptin levels *may* be ) |
| VEGF | Poor perfusion/cell starvation, Exercise intolerance, SOBOE, SOBAR | [Erythropoietin](#ErythropoietinProtocol) |
| C4a | Hypoperfusion, lactosis, low glutamate/glutamine on MR Spectroscopy  Brain fog, HA, myalgias, thermoregulation, Exercise intolerance | Actos/low amylose diet (Omega-3’s if Leptin <7), VIP |
| C3a |  | Actos/low amylose diet (Omega-3’s if Leptin <7), VIP |
| Androgens |  | Actos/low amylose diet (Omega-3’s if Leptin <7), DHEA |

2) **Medication Effects;**

|  |  |
| --- | --- |
| Cholestyramine, Welchol | Absorbs Gut Toxins |
| BEG/Rifampin | Kills MARCONS |
| Actos | Lowers MMP9, TNF, PIE-1, Leptin |
| Losartan | Lowers TGF β-1 |
| [VIP](#VIPEffects) | Stabilizes aromatase, [fixes most CIRS](#VIPResults) issues. [Caution!](#VIPRestrictions) |
| [Erythropoietin](#ErythropoietinProtocol) [Dosing](#ErythropoietinDosing) | Increases VEGF, lowers C4a |
| DHEA | Corrects Androgens |

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1. **Summary of** [**Labs**](file:///F:\Dropbox\woundedhealersnc\Gov%20McCrory\Physician%20Wellness%20LLC\CAM\CIRS\Chart%252525252520Draw%252525252520Sheet%252525252520Macro-Enabled%252525252520Workbook.xlsm)**;**
   1. **Initial labs to draw (Draw Emboldened as Baseline)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Test:** | **Lab to use** | | **Specimen** | | **Code#** | **Dx Codes** | | **Ideal Value** | **Normal Range** | **Therapeutic Comments** | **Associated Comments** | |
| **ERMI** | [**http://www.mycometrics.com/**](http://www.mycometrics.com/) | |  | |  |  | |  | <2 |  | <http://www.survivingmold.com/diagnosis/hertsmi-2> | |
| **HLA (RS)** | **LabCorp 012542**  **Labcorp:** ACC 20001604256 HLA DRB, DQ Typing | | Lavender, Room Temp | | 012542 | 279.10, 377.34, 279.8 | | [(See Rosetta Stone document)](file:///C:\Users\Oenbrink\AppData\Local\Temp\Rosetta%20Stone%20for%20HLA%20Haplotyping.docx) | [PCF by SSOP; Rosetta Stone for HLA Haplotyping](file:///C:\Users\Oenbrink\AppData\Local\Temp\Rosetta%20Stone%20for%20HLA%20Haplotyping.docx) |  |  | |
| [**VCS**](file:///C:\Users\Oenbrink\AppData\Local\Temp\Biotoxin%20Illness.doc#_Hlk367278792 1,87216,87219,0,,VCS) | [**http://www.survivingmold.com/store1/online-screening-test**](http://www.survivingmold.com/store1/online-screening-test) | |  | |  |  | | Negative |  | Repeat any time condition worsens |  | |
| **VIP** | **LabCorp or**  [**Quest VIP**](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=920) | | Lav-freeze-Trasylol | | 010397 | 279.8, 286.5, 710.0 | |  | 23.0-63.0 pg/ml |  | Re-regulates inflammation, decreases PASP with exercise, increases VO2max | |
| **MSH** | **LabCorp or**  [**Quest MSH**](http://www.questdiagnostics.com/testcenter/BUOrderInfo.action?tc=6883&labCode=AMD) | | Lav-freeze-Trasylol | | 010421 | 253.2 | |  | 35-81 pg/ml | Must be kept >35; low levels cause slow recovery from infections, opportunistic infections, decreased ADH production, increases VEGF, ACTH and Cortisol | Deficiency causes hormonal issues, Sleep disorders (fatigue), Endorphin release (causing chronic pain), Temperature regulation problems, Malabsorption, leaky gut, IBS, WBC's lose regulation of cytokine response, | |
| **Leptin** | [**Quest Leptin**](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=90367) | | SST-freeze | | 90367x | 253.2 | |  | M; 0.5-13.8 ng/ml F; 1.1-27.5 | Actos/low Amylose | Leptin <2 greatly reduces MSH, Rises on Post-Exposure day 2 | |
| ADH | [Quest ADH](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=252) | | Lav-freeze | | 252x | 253.2 | |  | 1.0-13.3 pg/ml | Parallels Osm; usually both are low (dehydration); if edema co-exists, suspect C4a elevations | In CIRS, Osm decreases before ADH decreases | |
| Serum Osmolality | [Quest Serum Osmolality](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=677) | | SST-freeze | | 677x | 253.2 | |  | 280-300 mosmol | DDAVP Corrects |  | |
| ACTH | LabCorp or  [Quest ACTH](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=211) | | lav-freeze | | 004440 | 255.41 | |  | 8-37 pg/ml |  |  | |
| Cortisol | [Quest Serum Cortisol](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=367) | | SST-freeze | | 367x | 255.41 | |  | AM 4.3-21.0 µg/dl PM 3.1-16.7 | Dysregulation with ACTH corrects with therapy |  | |
| DHEAS | [Quest DHEA Sulfate](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=402) | | SST-freeze | | 402.x | M257.2 F 256.39 | |  | by gender |  |  | |
| Testosterone | [Quest Total Testosterone](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=19958) | | red top-room temp | | 15983x | M257.2 F 256.39 | |  | By gender | Check Testosterone/Estrogen Ratio |  | |
| Androstenedione | [Quest Androstenedione](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=17182) | | SST-freeze | | 17182x | M257.2 F 256.39 | |  | by gender | No Aromatase Inhibitors if MSH <35 |  | |
| Estradiol | [Quest Estradiol](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=4021) | | Red-freeze | | 82671 | M257.2 F 256.39 | |  | [Reference Range](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=4021) |  |  | |
| Estriol | [Quest Estriol](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=34883) | | Red-freeze | | 82671 | M257.2 F 256.39 | |  | [Reference Range](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=34883) |  |  | |
| Estrone | [Quest Estrone](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=23244) | | Red-freeze | | 82671 | M257.2 F 256.39 | |  | [Reference Range](http://www.questdiagnostics.com/testcenter/BUOrderInfo.action?tc=23244&labCode=AMD&fromPage=BUOrderinfo&fromPageKeyword=Estradiol%20and%20Estrone) |  |  | |
| Progesterone | [Quest Progesterone](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=17183) | | Red-freeze | | 84144 | M257.2 F 256.39 | |  | [Reference Range](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=17183) |  |  | |
| CRP | LabCorp or  [Quest CRP](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=10124) | | SST-room temp | | 006627 | 378.54 | |  | 0.0-4.9 mg/L |  |  | |
| ESR | Here | | Lav | | 86140 | 790.1 | |  | 0-30 mm/hr |  |  | |
| **TGF β-1** | **LabCorp 905036** | | Lav Freeze (chilled tube/platelet poor plasma) | | 905036 | 286.5, 279.8, 210.0 780.79 | |  | 0-2,380 pg/ml | Losartan, exp3179 Consider VIP therapy to reduce TGF β-1 also work well | High is bad; Indicates remodeling/autoimmunity suppression/when TIGF lowered, autoimmunity resolves, down regulates VEGF, elevations cause ANCA rise reflects cellular immunity, affects lung, brain, immune systems | |
| **MMP-9** | **LabCorp 500124** | | SST-freeze | | 500124 | 340, 780.79 | |  | 85-332 ng/ml |  |  | |
| PAI-1 | LabCorp or  [Quest PAI-1](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=36555) | | Blue Freeze | | 146787 | 437.6, 286.5, 279.8 | |  | 2-14 IU/ml | Actos/low Amylose | Rises due to cytokine release, reflects inflammation in many tissues, rises in <2-3d of exposure to toxin | |
| Lipid Pheno (RS) | LabCorp | | SST-room temp | | 033886 | 272.0 | |  |  | Actos/low Amylose | With MMP9 increases clotting | |
| WBC | Quest | | Lav-room temp | | 6399x | 285.0 | |  | 5-10 |  |  | |
| Hb | Quest | | Lav-room temp | | 6399x | 285.0 | |  | 10-14 |  |  | |
| Hct | Quest | | Lav-room temp | | 6399x | 285.0 | |  | 30-45 |  |  | |
| Plt | Quest | | Lav-room temp | | 6399x | 285.0 | |  | 150K-450K |  |  | |
| CMP | Quest | | SST-room temp | | 10231x | 780.79 | |  |  |  |  | |
| GGT | Quest | | SST-room temp | | 482x | 250.00 | |  | 0-65 IU/L |  |  | |
| [**Nasal Culture**](http://www.dlmlabs.com/) | <https://www.dxos.com/mold-illness-testing/> | | Room temp | | DLM | 478.19 | |  |  |  |  | |
| **VEGF (Plasma)** | [**Quest VEGF Vascular Endothelial Growth Factor**](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=14512) | | Lav-freeze | | 14512x | 416.9, 253.2, 710.0 | |  | 31-86 pg/ml | BEG Spray + Rifampin 300 mg 2/AM X 1 month | Produces exotoxins that split MSH/don't survive if adequate MSH, Hemolysins that start Cytokine response, Lower T-Reg counts | |
| Erythropoietin | [Quest Erythropoietin](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=427) | | Red-freeze | | 427x | 285.9 | |  | 9-19.5 mU/ml | Actos/Low Amylose diet, Omega-3's, and/or VIP increases VEGF | Is low in CIRS, causing diminished VO2/cap hypoperfusion/SOB/fatigue/cramps | |
| Anticardiolipins (RS) | [Quest Anti-Cardiolipin Ab's IgM, IgG](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=36333) | | SST-freeze | | 7352x | 710.0 | |  | IgA 0-12, IgG 0-10, IgM 0-9 |  |  | |
| **AGA, IgA, IgG (RS)** | [**Quest Anti-Gliadin Ab's IgA, IgG**](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=8889) | | SST-freeze | | 8889x | 579.0 | |  | IgA IgG |  | Increases with CIRS | |
| Get Tissue Trans Glutaminase IgA, IgG, IgM if Gluten (+) | [Quest Tissue Transglutamase IgA, IgG](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=11073) | |  | |  |  | |  | 20-100U | 3 month no gluten diet and re-test | Increases with CIRS | |
| **C3a (not Futhan)** | [**Quest C3a**](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=17689) | | Lav-freeze | | 42003 | 279.8, 286.5, 710.0, 780.79 | |  | <940 ng/ml |  |  | |
| **C4a (not Futhan)** | [**Quest C4a**](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=19956) | | Lav-freeze | | 42658 | 279.8, 286.5, 710.0, 780.79 | |  | <2,830 ng/ml | Organisms in bloodstream, lowered by VIP therapy & Rx for CIRS, increases within 12 hours | Recheck C3a and C4a monthly in early treatment of PSL, consider high-dose statins with CoQa in PSL | |
| IgE | [Quest IgE](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=18877) | | SST-freeze | | 542x | 493.01 | |  | 33 U/ml | Consider VIP therapy; Erythropoietin 8,000 units twice/week for 5 doses | Good indicator of mycotoxins, Brain fog, Capillary Hypoperfusion | |
| Lyme WB (RS) | LabCorp or  [Quest Lyme WB](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=6646) | | SST-freeze | | 163600 | 088.81, 780.79 | |  | Negative |  |  | |
| CD4+ 505008  CD25+ | LabCorp 505008 | | lav-room temp | | 56880 | 280.79, 286.5, 279.8 | |  | >18% |  |  | |
| Lipase | [Quest Lipase](http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=606) | | SST-freeze | | 606x | 577.8, 780.79 | |  | <60u/L | Low with high TGF β-1 |  | |
|  | |  | |  | | |  | | | | |

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1. **Summarized Treatment Overview;**
   1. Remove from exposure
   2. Cholestyramine for 30 days
      1. Actos run-up if Lyme)
   3. Eradicate biofilm formers/MARCoNS
   4. No gluten if AGA (+)
      1. Do Tissue Trans Glutaminase IgA, IgG, IgM if Gluten (+)
         1. Expect to find more of the IgG than IgM but measure all 3
   5. Actos/low Amylose diet for MMP9, PAI-1, Leptin
   6. Correct ADH/Osmolality;
      1. Use DDAVP if abnormal
   7. Androgens;
      1. Look at Testosterone/Estrogen ratio’s to determine if up-regulated
      2. Consider DHEA Sulfate to correct from “upstream”
      3. Avoid Aromatase Inhibitors
   8. Fix C3a, C4a, TGF β-1
      1. Losartan
      2. Consider VIP therapy
   9. Check VEGF
      1. Consider Erythropoietin

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1. **Summary of Medications Used to Treat CIRS**;

|  |
| --- |
| [**Medications used to Treat CIRS**](file:///F:\Dropbox\woundedhealersnc\Gov%20McCrory\Physician%20Wellness%20LLC\CAM\CIRS\Chart%2525252520Draw%2525252520Sheet.xlsx#Medications!A1) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Medications used to Treat CIRS** |  |  |  |  |
| **Medication** | **Dose** | **Indication** | **Desired Effect** | **Comments** |
| Cholestyramine | 1 qid; Pediatric 60 mg/kg tid until VCS normalizes | Acute Toxins | Binds toxins in gut | May be used together |
| Welchol | 1 qid | Acute Toxins | Binds toxins in gut |  |
| Rifampin | 2X300 q AM | MARCoNS | Kills with BEG |  |
| BEG Spray | 2 puffs bid | MARCoNS | Kills with Rifampin | Hopkinton Rx |
| Actos/Low Amylose |  | Dysregulation of 1. MMP9/ADH-Osm/Androgens | Lowers MMP-9, blocks cytokine production, raises VEGF | If Leptin >7 |
| Omega-3 | 1.8 gm DHA/d and 2.4 gm EPA/d |  | Lowers MMP-9, blocks cytokine production, increases TGF β-1 (bad) & VEGF (good) | If Leptin <7 |
| DHEA | 2.4 EPA, 1.8 DHA Daily |  | Sex-steroid replenisher |  |
| DDAVP | 1-2 puffs qd or bid | Elevated ADH/Serum osmolality | Lowers elevated ADH/Osm serum | Corrects chronic dehydration, monitor serum Na |
| Losartan, exp3179Start low; 25 bid | Start low; 25 bid | High TGF β-1 | Decreases TGF β-1 |  |
| Erythropoietin | 8,000 U twice/wk X 5 doses | Increases VEGF | Lowers C4a, Angiogenesis, raises VEGF and increases VO2max | Protocol; Baseline TGF β-1, C4a, D-Dimer, CBC a. If Hb goes >16.5, it’s to high (FDA doesn’t want it >10) b. Ensure informed consent is signed c. Record the Lot Number |
| **VIP** | 2 qid-2/d | High TGF β-1, C4a; Increases T-Regs; Lowers C3a, C4a, TGF β-1, Reduces PASP with exercise, Increases VEGF and VO2max, Stabilizes aromatase and Vitamin D | Clinical Results of VIP Trial XIII H on Biotoxin Illness.doc | Magic! Must have abn VCS, No MARCoNS, ERMI<2 and MSH <35, Document Lipase, Monitor labs to show efficacy. Before giving VIP, draw baseline Lipase, VEGF, C4a, TGF β-1; Recheck 1 month, possibly monthly, trial lower dose after 6 months |

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[References of Dr. Berndston](http://www.slideshare.net/keithberndtson/mold-toxicity-syndrome-cirs)

**High C4a, Low C3a**

Zhou W. The new face of anaphylatoxins in immune regulation. *Immunobiology*. 2012;217(2):225-34 (C3a up-regulates Th2-driven antibody responses to foreign particles. We await more research into C4a-

specific effects on the activation or inhibition of Th1, Th2, Th17, and/or T reg cell activities).

**High MMP-9**

Romi F, Helgeland G, Gilhus NE. Serum levels of matrix metalloproteinases: implications in clinical neurology. *European Neurology.* 2012;67(2):121-8 (MMP-9 levels correlate with multiple sclerosis activity

and ALS neurodegenerative activity).

**High TGF β-1**

Han G, Li F, Singh TP, Wolf P, Wang XJ. The pro-inflammatory role of TGF beta-1: a paradox? *International Journal of Biological Sciences*. 2012;8(2):228-35. (TGF beta-1 has both pro-inflammatory [Th17, Th2] and

anti-inflammatory [Foxp3-induced CD4+CD25- T reg cells]).

**Low MSH**

Catania A, Lonati C, Sordi A, Carlin A, Leonardi P, and Gatti S. The melanocortin system in control of inflammation. *The Scientific World Journal*. 2010;10:1840–1853. (MSH and ACTH are melanocortin peptides. MSH reduces overactive immune responses in various tissues).

**Low ADH**

Aguilera G, Rabadan-Diehl C. Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. *Regulatory Peptides*. 2000;96(1-20;23-9 (Low ADH [vasopressin] levels

reduce stress adaptation capacity by lowering cortisol and kidney water conservation capacity).

**Low or High VEGF**

Mayer G. Capillary rarefaction, hypoxia, VEGF, and angiogenesis in chronic renal disease. *Nephrology, Dialysis, and Transplantation*. 2011;26(4):1132-7 (If VEGF induced hypoxia counter-regulatory factors can exert beneficial or harmful effects in chronic kidney disease, they likely do so in other tissues as well).

**Low VIP**

Shoemaker RS, House D, Ryan JC. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. *Health.* 2013;5(3):396-401 (VIP is a regulator of immune, oxygenation, and blood flow functions).

**Low T reg cells**

Goldstein JD, Perol L, Zaragoza B, Baeyens A, Marodon G, Piaggio E. Role of cytokines in thymus-derived vs. peripherally derived regulatory T cell differentiation and function. *Frontiers in Immunology*. 2013;4:155. (TGF-beta can shift activity from T regs to Th17 cells. C3a-C4a-C5a also play a role).

[Expanded CIRS Bibliography of >500 Peer Reviewed References.](http://www.paradigmchange.me/cfs-info/me-and-cfs-medical-abnormal/me-cfs-and-medical-abnormal.pdf)

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